Congenital Heart Disease, Type 1 and Type 2 Diabetes Mellitus

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The scientific
news of today,
the history of
tomorrow

ABSTRACT

Worldwide, 1% of all live born children are born with a congenital heart disease (CHD) and currently >95% reach adulthood due to better diagnostics and medical care. At the same time, Diabetes mellitus (DM), type 1 (T1DM) and type 2 (T2DM), is increasing worldwide. The incidence of the endocrine disease T2DM, which makes up more than 90% of all diabetes increases in particular and is part of the metabolic syndrome. T2DM is due to a decrease in insulin sensitivity and insulin production depending on genetic factors as well as obesity and a sedentary lifestyle. T1DM is an autoimmune disease that can develop due to i.e. genetic factors, exposure to infections and stress-strain leading to an autoimmune response.

The incidence of T1DM in patients with CHD is unknown and the incidence of T2DM in patients with CHD is previously not extensively studied. Also, the effect of T1DM and T2DM in the CHD population on mortality is unknown.

The aim of this thesis was to in large reliable registers and cohorts investigate the prevalence and incidence of T1DM and T2DM in a CHD population, and how this influences the mortality and morbidity in patients with CHD and T1DM and T2DM.

Paper I, a retrospective comparative cohort study, investigated the risk of concurrent CHD in patients with T2DM, regarding T2DM onset, mortality and morbidity compared with patients with T2DM without CHD. The study combined data from the National Diabetes Register (NDR), National Patient Register (NPR) and the Cause of Death Register (CDR).

Out of patients with T2DM, 833 patients with CHD were matched with 5 controls without CHD, matched by sex, year of birth and year of entry in to the NDR.

CHD patients had significantly lower body mass index (BMI), higher creatinine and were more sedentary as compared to patients with T2DM but without CHD. The overall mortality was 26.2% for CHD patients as compared with 19.9% (P<0.001) for the control group, and five-year mortality rates were 5.2% for patients with CHD and T2DM compared to 3.4% (P=0.014) in the controls.

In conclusion, CHD and secondary risk factors for cardiovascular disease frequently coexist and the development of T2DM in the adult CHD population is not uncommon with an estimated prevalence of between 4 and 8%. Treatment of conventional cardiovascular risk factors in patients with CHD could be considered important given the relatively high morbidity and high risk for mortality observed in patients with the combination of CHD and T2DM.

Paper II, a retrospective comparative cohort

study investigated the risk of concurrent CHD in patients with T1DM, regarding T1DM onset, mortality and morbidity compared to patients with T1DM without CHD. The study combined data from the National Diabetes Register (NDR), National Patient Register (NPR) and the Cause of Death Register (CDR).

Out of patients with T1DM, a total of 104 patients with CHD were matched with 520 controls without CHD, matched by sex, year of birth and year of entry in to the NDR. Patients with CHD and T1DM had an earlier onset of diabetes (13.9 vs. 17.4 years, P<0.001), longer duration of T1DM (22.4 vs. 18.1 years, P<0.001), higher prevalence of retinopathy (64.0 vs. 43.0%, P=0.003), higher creatinine levels (83.5 vs. 74.1 μmol/L, P=0.03) and higher mortality (16 vs. 5%, P=0.002). Patients with CHD and T1DM had a higher rate of co-morbidities, expressed as a higher number of hospitalizations per patient (5.28 vs 3.18 P=0.007) with a discharge diagnosis of CHD, IHD, heart failure (9% vs. 2%, P=0.02), atrial fibrillation, stroke (6% vs. 2%, P=0.048), PCI, CABG, or renal failure, after onset of T1DM compared with controls.

In conclusion, from a nationwide register of patients with T1DM, the coexistence of CHD and T1DM was associated with an earlier onset of T1DM, a higher frequency of microvascular complications, co-morbidity, and mortality.

In paper III, a retrospective comparative cohort study performed by combining registers (NPR and CDR), the incidence of T1DM and the mortality was analysed in patients with CHD by birth cohort (1970-1993, 1970-1984 and 1984-1993). Patients with CHD were matched with population-based controls matched for sex and year of birth without CHD and followed from birth until a maximum of 42 years.

Among 21,982 patients with CHD, 221 patients developed T1DM and among 219,816 matched controls 1,553 patients developed T1DM . The hazard ratio (HR) for developing T1DM was 1.50 (95%, CI 1.31-1.73) in patients with CHD compared to the controls. The first birth cohort (1970-1984) had the highest risk for developing T1DM, HR 1.87 (95%, CI 1.56-2.24). After T1DM onset, the mortality risk was 4.21 times higher (95%, CI 2.40-7.37) in patients with CHD and T1DM compared to controls with T1DM without CHD.

In conclusion, a nationwide cohort of patients with CHD and controls, the incidence of T1DM onset was 50% higher in patients with CHD, indicating a significant increase in risk among birth cohort 1970-1984. A four-fold increase in mortality among patients with CHD and T1DM was seen compared to controls with only T1DM.

In paper IV, a retrospective comparative cohort study combining registers (NPR and CDR) analysed the incidence of DM and the mortality in patients above 35 years of age with CHD. The CHD population was compared with population-based controls matched for sex and year of birth without CHD, divided by birth cohort, CHD lesion cohort and gender cohort, and followed from birth until a maximum of 87 years of age.

Out of patients with CHD who survived until at least 35 years of age without developing DM, 8,4 % had an onset of DM after 35 years of age compared to 5.6% of the matched controls. The risk for developing DM was significant increased in patients with CHD compared to the controls and the second birth cohort (1960-1983) had the

highest risk for DM. The risk of DM increased with complexity of CHD. After DM onset, mortality was significantly higher in patients with CHD and DM compared to controls with DM without CHD.

In conclusion, from a nationwide cohort of patients with CHD and controls, the incidence of developing DM was significant higher in patients with CHD, showing a significant increase in risk also divided by birth cohort and by CHD lesion. The combination of CHD and DM was associated with a significantly increased mortality compared to controls without CHD.

In conclusion, this thesis show that the CHD population do have a higher risk of T1DM and T2DM compared with the general population. Whether this is due to environmental risk factors or due to genetics needs to be further studied. Patients with CHD also have a higher mortality and morbidity after onset of DM compared with controls without CHD indicating that the combination of CHD and DM are more lethal than each diagnosis on its own. These findings are of great importance in future preventive and medical care for patients with CHD.

Keywords: Congenital Heart Disease; CHD; Diabetes Mellitus; DM; Type 2 Diabetes Mellitus; T2DM; Type 1 Diabetes Mellitus; T1DM; cardiovascular risk factors; CVD; lifestyle factors; genetics; obesity; metabolic syndrome; morbidity; mortality; complications; epidemiology

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SAMMANFATTNING PÅ SVENSKA

Omkring 1 % av alla barn som föds i världen idag, föds med ett medfött hjärtfel (CHD) och idag överlever över 95% av alla med medfött hjärtfel till vuxen ålder. Detta på grund av förbättrad diagnostisering och medicinsk vård.

Samtidigt ökar förekomsten av Diabetes Mellitus (DM), typ 1 (T1DM) och typ 2 (T2DM), globalt. Särskilt ökar insjuknandet av T2DM som är en endokrin sjukdom och som utgör mer än 90 % av all DM. T2DM är en del av det metabola syndromet med insulinresistens och minskad insulinproduktion beroende på genetiska faktorer och livsstilsfaktorer som övervikt och stillasittande livsstil. T1DM är en autoimmun sjukdom som kan bero på genetiska faktorer, infektionssjukdomar och fysiska stressfaktorer som triggar en autoimmun reaktion. Personer med medfött hjärtfel genomgår mer inneliggande sjukvård, kirurgi och fysiska stressfaktorer än den allmänna populationen utan medfött hjärtfel, vilket skulle kunna bidra till en autoimmun reaktion och ökad risk för T1DM.

Med en ökande livslängd i patientgruppen med medfött hjärtfel ökar också ålderssjukdomar samtidigt som det finns det en risk för en mer stillasittande livsstil för dessa patienter. T2DM ökar i samhället på grund av mer stillasittande och andra livsstilsfaktorer och patienter med medfött hjärtfel skulle kunna vara extra utsatta för ökad risk för T2DM på grund av detta.

Avhandlingen har till syfte att i stora nationella register studera förekomst, insjuknande, samsjuklighet och dödlighet hos patienter med medfött hjärtfel i kombination med T1DM eller T2DM i olika kohortstudier, vilket inte har gjorts tidigare. Metodiken är epidemiologiska retrospektiva kohortstudier utförda på stora nationella register.

Resultaten visar på ett ökat insjuknande i DM, ökad samsjuklighet och dödlighet hos patienter med medfött hjärtfel jämfört med kontroller matchade på kön och ålder. För patienter med medfött hjärtfel jämfört med matchade kontroller, var risken att insjukna i T1DM 50% högre hos patienter med medfött hjärtfel. Kombinationen av medfött hjärtfel och T1DM var associerad med en fyrfaldig ökning av dödlighet jämfört med kontroller med endast T1DM. Samexistensen av medfött hjärtfel och T1DM var förknippad med ett tidigare insjuknande av T1DM, en högre frekvens av mikrovaskulära komplikationer, samsjuklighet och dödlighet jämfört med kontroller med T1DM utan medfött hjärtfel.

Samtidigt var risken att insjukna i DM efter 35 års ålder 50% större hos personer med medfött hjärtfel jämfört med matchade kontroller utan

hjärtfel och ökade med komplexitet av hjärtfel. Efter insjuknande i DM efter 35 års ålder var dödlighetsrisken signifikant högre hos patienter med kombinerad medfödd hjärtsjukdom och DM jämfört med kontroller med DM utan medfött hjärtfel. Personer med medfött hjärtfel och T2DM hade också ett mer stillasittande liv, högre dödlighet och högre frekvens av mikrovaskulära komplikationer jämfört med kontroller med T2DM utan medfött hjärtfel.

Dödligheten hos patienter med medfött hjärtfel är ökad jämfört med befolkningen utan hjärtfel, och kombinationen av medfött hjärtfel och DM ökar dock dödligheten ytterligare. Dessa upptäckter är av stor betydelse för preventiv och medicinsk vård för patienter med medfött hjärtfel.

LIST OF PAPERS

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

I. Dellborg M, Björk A, Pirouzi Fard N M, Ambring A, Eriksson P, Svensson A-M, Gudbjörnsdottir S.
High mortality and morbidity among adults with congenital heart disease and type 2 diabetes
Scand Cardiovasc J. 2015;49(6):344-50.

II. Björk A, Svensson A-M, Pirouzi Fard N M, 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 May 29:1-8

III. Björk A, Mandalenakis, Z, Giang W K, 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
Int J Cardiol 2020 10 Jan, in print

IV. Björk A, Mandalenakis, Z, Giang W K, Rosengren A, Eriksson P, Dellborg M.
Incidence of Diabetes Mellitus and Morbidity in Patients with Congenital Heart Disease – A Nationwide Cohort Study.
In manuscript

CONTENT

ABBREVIATIONS

CHD	Congenital Heart Disease/Defect
ACHD	Adult Congenital Heart Disease/Defect
GUCH	Grown Ups with Congenital Heart Disease
DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glycaemia
LADA	Latent Autoimmune Diabetes in Adults
MODY	Maturity Onset Diabetes in Young
NDR	National Diabetes Register
NPR	National Patient Register
CDR	Cause of Death Register
PIN	Personal Identity Number
PRN	Personal Registration Number
CVD	Cardio Vascular Disease
RTP	Register of Total Population
SWEDCON	Swedish Congenital Heart Disease Register
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
HF	Heart Failure
AF	Atrial Fibrillation
IHD	Ischemic Heart Disease
BMI	Body Mass Index

1 INTRODUCTION

1.1 SOME WORDS ABOUT EPIDEMIOLOGY

Epidemiology, the word comes from the Greek word epi, meaning on or upon, demos, meaning people, and logos, meaning the study of. It could be defined as the study (scientific, systematic, data-driven) of the distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states or events in specified populations, and the application of this study to the control of health issues[1]. Epidemiology is the core science of public health[2] and an essential scientific methodology in this thesis on the study of the risk of Diabetes Mellitus (DM) in the Congenital Heart Disease (CHD) population.

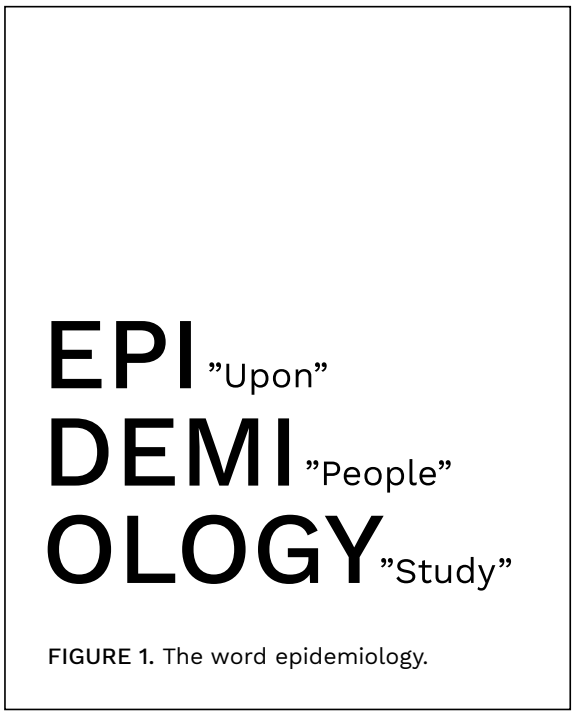


FIGURE 1. The word epidemiology.

1.2 ASSOCIATION AND CAUSALITY

Causality is the relation between cause and effect. In epidemiology the aim is to assess the cause of outcome and in medicine often related to the disease. The word cause is associated with making a difference and as epidemiology is a science it aims to discover the health states such as health outcomes/effects[3]. However, since most epidemiological studies are observational rather than experimental, correlation or association does not always mean causality in statistical terms. An association, defined as a state were two variables (e.g. A and B) occur together more or less often than expected by chance. If an association is applied that does not always mean that there is a direct link (i.e. causality) between the two variables and the research aim is to prove, if there is any, causality between exposure and outcome.

One famous example of this is a paper of a case-control study that Doll and Hill et al. published in 1950, showing that smokers (exposures) had a more frequent onset of lung cancers (outcome), revealing a significant epidemiological association between smoking and lung cancer but not a causality on what determinants that caused cancer[4]. A number of possible explanations for an observed association need to be considered before a cause-effect relationship is known to exist. Later on, Hill introduced the causality criteria, 9 epidemiological criteria to determine whether an observation shows an association or a causality (Table 1)[5].

TABLE 1. The Bradford Hill epidemiological criteria for causality

Number	Criteria	Explanation
1	Strength	Statistically strong association between exposure and outcome, the more likely the relationship is to be causal.
2	Consistency	Has the outcome and association been repeated by other research groups?
3	Specificity	How generalizable is the association? Particular exposure gives outcome.
4	Temporality	Exposure must precede outcome.
5	Biological gradient	Dose-response curve can be detected.
6	Plausibility	Is there a plausible mechanism between the exposure and the outcome? Does it seem likely?
7	Coherence	Coherence between epidemiological and laboratory findings.
8	Experiment	Do experimental data support the association? Removal of exposure changes outcome?
9	Analogy	The effect of similar factors under same circustances may be considered.

However, these guidelines for causality are important to have in mind but are not always applicable to epidemiologic research. Rothman assert that the only criterion that is truly a causal criterion is 'temporality', that is, that the cause preceded the effect[2].

With that being said, the observed association may in fact be due to the effects/exposures of one or more of random (chance) or systematic errors (Fig 2.)

Systematic error or bias can be divided into three groups; selection (selection and inclusion of participants is done in such a way that the groups are not comparable), information (non-differential misclassification or differential misclassification) or confounding (a third variable which is related to both exposure and outcome that influence exposure to outcome and is an intermediate variable) errors. Confounders can be handled by study design and knowledge about which confounders may be relevant in the study. Common confounders could be gender, socio-economic status, profession, education etc. In epidemiological studies, restriction of participants in the study population or matching of cases and controls are often used strategies to get around this problem. Other models that can be used to adjust for confounders are stratification and multivariable models[2, 6].

The process of causal inference is complex, and arriving at a tentative inference of a causal or non-causal nature of an association is a subjective process[2]. Epidemiological research can only show associations but not causality, however that does not mean it is not clinically significant and true and some of the causality criteria are often used in epidemiological studies to support this[5].

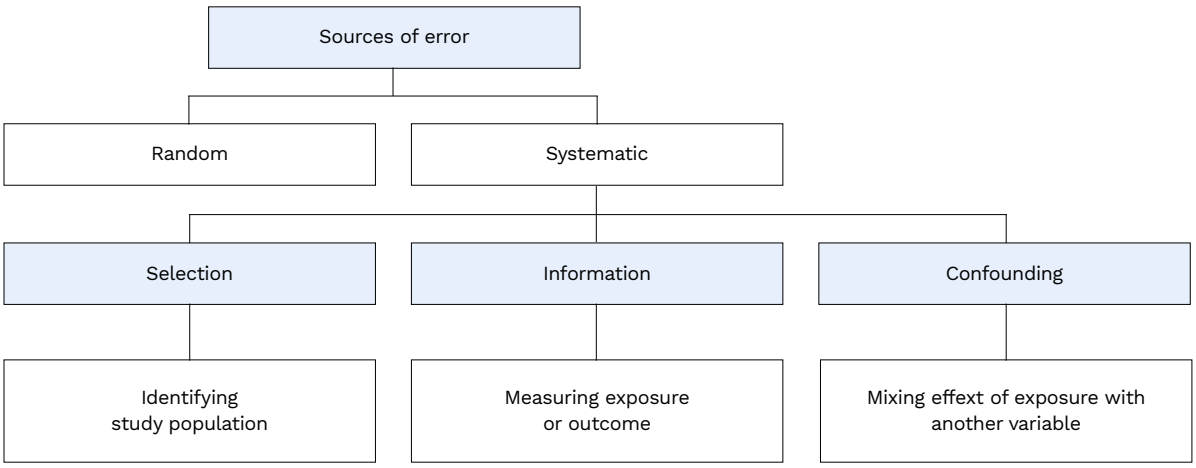


FIGURE 2. Sources of error.

1.3 STUDY DESIGN

The study design of the epidemiological study depends on what is known, the research questions, outcome, exposure, time and cost, advantages and disadvantages (Fig. 3).

The non-experimental, individual based, analytical epidemiology studies in this thesis are done on large registers were the starting point is a specific population within which the exposure is characterized, a cohort, and they are then investigated over time to determine whether the exposure affects the risk of the outcome. The cohort is divided in cases, primary exposed, and controls, non-exposed. A cohort study design could be prospective (observing the group from a specific date and onward) or retrospective (looking back at historical data). In these studies, it is of importance to have knowledge and be aware of if there could be other exposures, confounders, that could affect the outcome since there is only access to register health care data and the opportunity to conduct prospective analyzes is limited or none.

1.4 MEASURING OUTCOME

To be able to describe the outcome there are different tests to measuring outcome for different analyses. The incidence (person per time) which refers to the number of new affected persons per unit of time or population, or the prevalence (proportion) which refers to the status number present at any time point, are often used. The description in a paper is often presented to get a baseline and background about the material of the study where focus is often on the baseline, exposure and confounders. In a cohort design study when analyzing data, incidence or odds are often calculated to describe a measure of association between exposure and outcome (e.g. disease occurrence) while risk ratio, rate ratio or odds ratio are measures for comparing exposure and outcome (e.g. comparing disease occurrence) (Table 2).

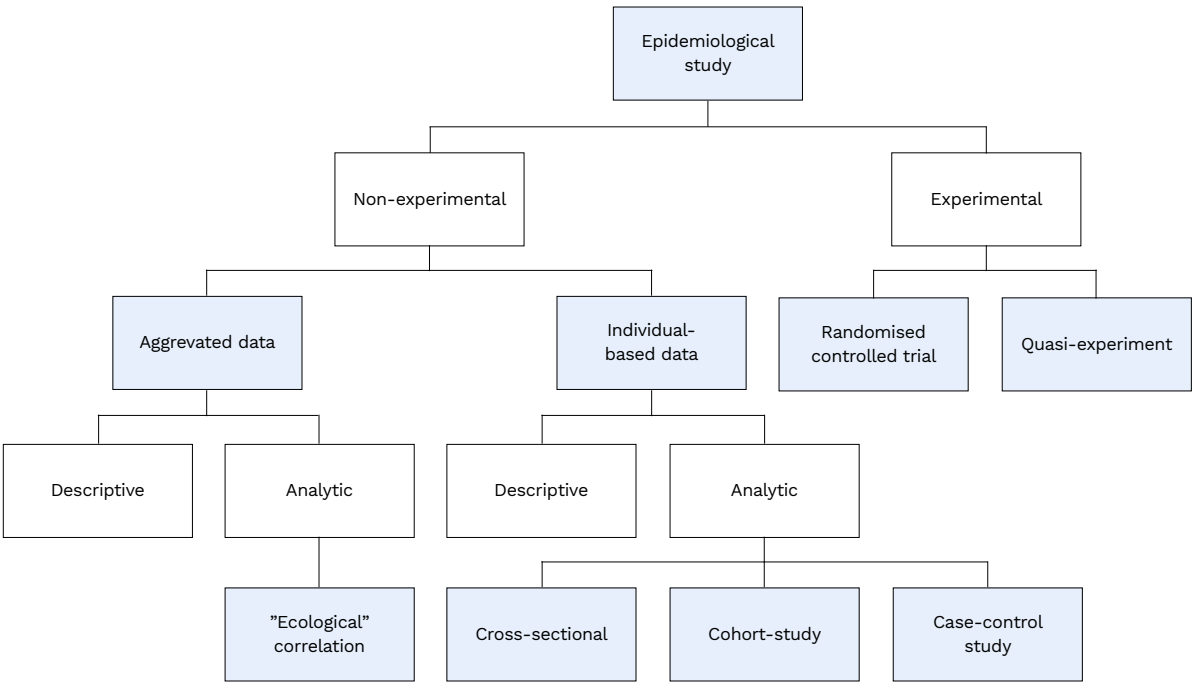


FIGURE 3. Epidemiological study design.

TABLE 2. Study design and measurements.

Study design	Measures of disease	Measures for occurrence comparing disease occurence
Experimental	Cumulative incidence, incidence rate, or odds	Risk Ratio*, Rate ratio* or Odds Ratio
Cohort	Cumulative incidence, incidence rate, or odds	Risk Ratio, Rate Ratio or Odds Ratio
Case-control	-	Odds Ratio
Cross-sectional	Prevalence	Prevalens Ratio, Prevalence Odds Ratio
Ecological	Incidence rate	Rate Ratio

*Relative Risk

The result of study design could be seen as positive if there is a significant difference or negative if there is a non-significant difference. The result could also be inconclusive if there is not a detectable difference or a difference but it is because of "interruptions/bias (e.g. for a small selection of "power problems", misclassifications etc.)(Table 3).

1.5 CONGENITAL HEART DISEASE – THE STUDY POPULATION

Congenital heart disease (CHD) is the most frequent malformation among live born infants as well as a major cause of death during infancy and in young children [7-13]. International studies report that about 1% of all live born children are born with a CHD [14-16]. The number has been

TABLE 3. Example of statistical tests for different situations.

Type of groups	Measurement (from Gaussian Population)	Rank, Score, or Measurement (from Non- Gaussian)	Binomial (Two Possible Outcomes)	Survival Time
Describe one group	Mean, SD	Median, interquartile range	Proportion	Kaplan Meier survival curve
Compare one group to a hypothetical value	One-sample t-test	Wilcoxon test	Chi-square or Binomial test	
Compare two unpaired groups	Unpaired t test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel
Compare two paired groups	Paired t test	Wilcoxon test	McNemar's test	Conditional proportional hazards regression
Compare three or more unmatched groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox proportional hazard regression
Compare three or more matched groups	Repeated-measures ANOVA	Friedman test	Cochrane Q	Conditional proportional hazards regression
Quantify association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients	

stable over time and across countries [17-19], however a recent global study presented the CHD prevalence at birth to be 1.7 % indicating that this number could be modified in the future due to improved diagnostics [20].

CHD has been defined as proposed by Mitchell et al.[21], as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance." This definition excludes functionless abnormalities of the great veins, or of the branches of the aortic arch. CHD usually excludes congenital arrhythmias as well as hypertrophic or dilated cardiomyopathy. Patients with severe connective tissue disorders, such as Marfan's syndrome or Ehlers-Danlos type IV syndrome, are often considered to have a CHD if they have a cardiac and aortic lesion[9].

1.5.1 CHD AND SEVERITY

There are about 200 different types of CHD and some of these are very rare[22]. To describe the diversity of CHD and to divide CHD by lesion, there are different strategies[10, 13, 23, 24]. What they all have in common is that they are somehow classified hierarchically by severity; complex CHD, moderate CHD and non-complex/mild CHD. However, the numbers diverse depending on how the classification is presented and how the study is done. According to Marellis et al. studies in Quebec 2010, of 45,960 patients with CHD, born between 1983-2000, 9.2 % of the adult patients with CHD had a severe CHD and 12.2 % of children [25]. In another study, Botto et al., of 4,703 cases of CHDs in the US with birth years 1997 through 2002, 63.6% were simple, isolated cases and 7.8 % had a severe CHD[23].

In table 4 some of the most common CHD are listed [9, 22, 24, 25].

TABLE 4. Some of the most common CHD, divided by lesion and presented as numbers in % of all CHD

CHD	Abbre-viation	Defect	N (%)	Discovered	Symtoms	Treatment	Follow-up
Patent Ductus arteriosus	PDA	Persistent connection between the aortic arch and the pulmonary artery in the fetus	3-8%	Infant-adult	Murmur	Inerventional catheterization, medication, surgery	1 year after treatment
Atrial Septal Defect	ASD	Hole between atria	10-30%	Infant-adult	Murmur, arrythmia	Surgery, interventional cardiac catheterization	Years after surgery
Ventricular Septal Defect	VSD	Defect of intraventricular septum, left to right shunt	20-40%	Infant-childhood	Murmur, heart failure	Surgery, interventional catheterization, none	Years after surgery
Atrio Ventricular Septal Defect	AVSD	ASD primum, complete atrio-ventricular defect	4-5%	Infant-childhood	Murmur, heart failure	Surgery	Through life
Coarction of the aorta	CoA	Aortic narrowing of aortic arch-descending aorta	2-4%	Infant-young adult	Upper body hypertension, weak or absent femoral pulses, heart failure	Surgery (infant) interventional catheterization (adult)	Through life
Tetralogy of Fallot	TOF	VSD+pulmonary stenosis+overriding aorta+right ventricular hypertrophy	1,5-4%	Infant-adult	Cyanosis, ventricular arrytmias	Surgery	Through life
Transposition of the great arteries	d-TGA	Transposition of the aorta and the pulmonary artery	2-5%	Infant	Cyanosis, ventricular arrytmias	Interventional catheterization (aucte, palliative), Surgery	Through life
Single ventricle defect	SV	Nondevelopment of one ventricle	1%	Infant	Cyanosis, heart failure	Surgery	Through life
Pulmonary Stenosis	PS	Narrowing of the pulmonary valve	5-7%	Infant-adult	Murmur, arrythmia, angina pectoris, synkopé	Expectancy-Interventional catheterization, surgery, none	Through life
Aortic stenosis	AS	Narrowing of the aortic valve	4%	Infant-adult	Murmur, syncope, heart failure	Surgery, interventional catheterization, none	Through life

When applicable in this thesis, the hierarchic classification was used for CHD stratification as described by Liu and modified by Botto (Table 5), a mapping strategy for most cardiac phenotypes and important subgroups of CHDs that may differ by etiology or mechanism [26, 27], consisting

of conotruncal defects (lesion group 1), non-conotruncal defects (lesion group 2), coarctation of the aortae (lesion group 3), ventricular septal defect (lesion group 4), atrial septal defect (lesion group 5) and other heart and circulatory system anomalies (lesion group 6).

TABLE 5. List of diagnosis according to CHD Botto classification and corresponding ICD codes

Lesion group	Diagnoses	ICD 8	ICD 9	ICD 10
1. Conotruncal defects	Common truncus	746	745A	Q200
	Aortopulmonary septum defect	746	745A	Q214
	Transposition of great vessels	746,1	745B	Q201-203
	Tetralogy of Fallot	746,2	745C	Q213
2. Nonconotruncal defects	Endocardial cushion defects	746,47*	745G	Q212
	Common ventricle	746,39	745E	Q204
	Hypoplastic left heart syndrome	746,74	746H	Q234
3. Coarctation of the aortae	Coarctation of the aortae	747,19	747B	Q251
4. Ventricular septal defect	Ventricular septal defect	746,39	745E	Q210
	Other congenital malformations of cardiac septa	746,89	745W	Q218
5. Atrial septal defect	Atrial septal defect	746,42	745F	Q211
		746,43		
		746,46		
6. Other heart and circulatory system anomalies	All diagnoses not included in the 5 specified categories above			

*Ostium AV communae

CHD is overrepresented among patients with chromosome and/or syndrome disorders. Of individuals with Down syndrome (trisomy 21), 40 % have a CHD, and 30 % of patients with Turner's syndrome. Marfan's syndrome, 22q11 deletion and Noonans syndrome are other disorders that are frequently reported with a CHD[22].

1.5.2 IMPROVED SURVIVAL IN PATIENTS WITH CHD

The proportion of patients with CHD reaching adulthood has increased since the 1960s and registered data indicate that 90-97% of these children nowadays at least reach 18 years of age, referred to as adult congenital heart disease (ACHD) [12, 28], with a prevalence of 4-5 per 1000 adults, due to increasing survival rates nowadays [12, 24, 25]. The increasing survival rates is due to improvements in clinical, medical, surgical, pre- and post-operative care, catheter intervention and centralized tertiary care [7, 9, 10, 12, 13, 24, 25, 28-38].

With an aging CHD population, the chronic diseases in this patient group increases and with that the medical interest of this complex and aging population. Therefor it is of utmost value for the care givers to gain knowledge and develop skills on how to work with this patient

group and to know what to be observant on and have in mind treating this complex patient group.

As the CHD population grow older they have been described to have an increased risk of CVD, morbidity and mortality [7, 39-45]. The risk of ischemic stroke in children and young adults with CHD was described to be 10.8 times higher compared to population-based controls without CHD in a large nationwide cohort study in Sweden. Cardiovascular comorbidities were strongly associated with the development of ischemic stroke in these CHD patients indicating the importance of monitoring these patients as they grow older[45]. In the same cohort, patients with CHD was described to have a 100-fold higher risk of developing heart failure (HF) compared with matched controls, up to 42 years of age. The highest risk of developing HF was described in patients with complex CHD, and in this group a 63% risk of death was seen compared with 11% in patients with CHD without HF [43].

In a large national cohort study, Mandalenakis et al. reported the risk of atrial fibrillation (AF) in children and young adults with CHD to be 22 times higher compared to population based matched controls. Up to the age of 42 years, 1 of 12 patients with CHD had developed AF, and 10 % of patients with CHD with AF had developed heart failure. The risk of AF increased with complexity of CHD with the highest risk in patients with conotruncal defects. This data suggest that with an aging CHD population, conventional risk factors may further add to this arrhythmia burden and that there is a need for preventive measures and anticoagulation treatment in patients with CHD [44]. At the same time, adult patients with CHD have an increased incidence of cancer, suggested owing to repeated radiation exposure, genetic predisposition, or repeated stress factors during heart interventions. From the same cohort, Mandalenakis et al. described children and young adults with CHD to have a 2-fold higher risk of cancer, with the highest risk in the group with complex heart lesions, e.g. conotruncal defects, compared to population-based controls without CHD. This suggest that a systematic screening for cancer could be considered for this at-risk group of patients[42].

Although, the relative risk of a CHD patient developing heart failure, stroke, cardiac rhythm disorders or other fatal or non-fatal complications is greatly increased compared to the general population, the absolute risk is very low[39].

1.5.3 GUCH AND ACHD

In 1960, the first specialty care for Grown Ups with Congenital Heart Disease (GUCH), also known as Adult Congenital Heart Disease (ACHD), was started in USA. In Sweden, the first GUCH-center was started in the middle 1990's and today there are two large central GUCH-centers, Gothenburg and Lund. These centers provide highly specialized tertiary care for adults with CHD, including surgery and intervention. There are also several smaller GUCH-centers scattered throughout the country. The GUCH-centers makes the transition from the pediatric cardiologist centers easy and smooth on the patients 18th birthday. The idea is that all records from the pediatric cardiologist should be transferred to a medical team consisting of cardiologists, nurses, physiotherapists, psychologists, etc. at the GUCH-center who continues to follow the patient and in many cases throughout life, which will contribute to a safe and optimized care for the patient[46].

1.6 DIABETES MELLITUS

Diabetes mellitus (DM) is a chronic disease which increases worldwide and more than 400 million people worldwide live with DM today[47], expecting this number to increase to 600 million people in 2030[48]. DM is characterized by hyper-glycaemia due to insufficient insulin secretion, impaired insulin action, or both. DM depends on a multiple aetiology and is upon this and its' clinical characterization classified as Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), Gestational Diabetes (GDM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glycaemia (IFG) and other specific forms of diabetes[47, 49, 50].

The definition of diabetes is as follows[47, 50]:

- HbA1c ≥ 48 mmol / mol (6.5%) on two occasions, or 1 together with elevated plasma(P) glucose (fasting (F) or after oral glucose loading) as follows:
    - FP-glucose level ≥ 7.0 (capillary or venous) mmol / l (126 mg/dL) on two occasions,
    - Non-fasting glucose level ≥ 11.1(capillary or venous) mmol/l (200 mg/dL) along with symptoms of hyperglycemia, or
    - Oral glucose tolerance test (OGTT) with 2h capillary value ≥ 12.2 mmol / l, venous value ≥ 11.1 mmol / l.

Associated long-term microvascular complications as retinopathy, nephropathy, neuropathy are associated and overrepresented in DM compared to the general population, as is also macrovascular damage, resulting in coronary heart disease, stroke and peripheral vascular disease, which is still the leading cause of death among DM patients [47, 51].

1.6.1 TYPE 1 DIABETES MELLITUS

T1DM, juvenile-onset diabetes or insulin dependent diabetes, characterized by an autoimmune mediated destruction of the insulin-forming beta cells, which leads to that insulin production ceases until only insignificant residues remain [50, 52, 53]. T1DM is one of the most common chronic diseases during childhood [54], although the incidence of T1DM varies by country [55]. The national annual incidence of T1DM among people aged younger than 25 years in Sweden is approximately 40/100 000 person years which give a prevalence of 1%[56-58]. In the US the prevalence of T1DM has been reported to be increasing and was approaching 2% in 2009 [59].

Increased exposure to infections, lifestyle changes, and increased biologic stress-strain can contribute to an autoimmune response and to an increased risk of developing T1DM [60].

T1DM almost exclusively occur in childhood and adolescence but could debut in adults although the proportion of adult onset are an insignificant size of the population. The incidence is highest between 5-14 years of age[50].

T1DM could not go undiscovered as it results in 2-3 weeks of polyuria, thirst, fatigue, weight loss and accommodation disorders and treatment

with insulin is henceforth a lifelong requirement. Biochemical markers of autoimmunity as Glutamic acid decarboxylase (GAD), protein tyrosine phosphatase (IA-2) and zinc transporter 8 (ZnT8) can be detected at onset in 60-80% of patients with T1DM. T1DM is also associated with other autoimmune diseases such as hypo- and hyperthyroidism, hashimotothyroidism, celiac disease, atrophic gastritis with pernicious anemia, Addison's disease and pituitary gland insufficiency.

Patients with T1DM have a significant risk increase of developing micro and macro vascular complications due to that the atherosclerotic process is enhanced. This is due to factors related to chronic hyper-glycaemia and insulin resistance, resulting in oxidative stress, increased inflammation, endothelial dysfunction, hypercoagulability and an increased atherogenic lipid profile[61-64]. The development of atherosclerosis (macroangiopathy) occurs more quickly in T1DM. Comorbidities and mortality due to cardiovascular disease (CVD) including coronary disease, stroke and peripheral vascular disease are 2-3 times higher in patients with T1DM compared to the general population, and increase sharply with the co-occurrence of nephropathy[50].

A study in the UK, based on 7,713 patients with T1DM from the General Practice Research Database (GPRD), 1992-1999, showed a 4-fold increased mortality in patients with T1DM compared to patients without DM from GPRD[65]. However, a recently published study based on the Swedish National Diabetes Register (NDR) with patients registered from 1998 through 2012 and followed to the end of 2014 showed that the mortality and the incidence of cardiovascular outcomes has declined substantially in later years among persons with diabetes compared to controls[66].

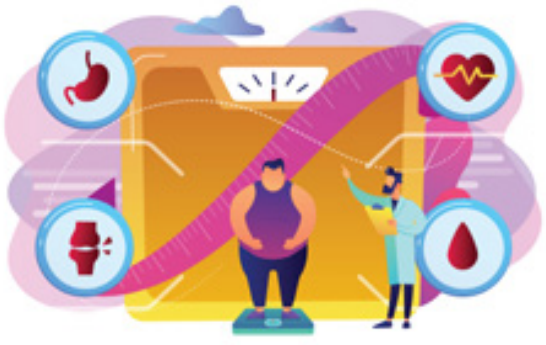
As in the general population, the improved survival in T1DM increases the life-risk for a cardiovascular event. Norhammar et al. described in a national cohort, that mortality for patients with T1DM referred for coronary angiography is influenced by numbers of affected coronary vessels. Indicating the need for early intensive prevention of coronary artery disease in these patients[67].

1.6.2 TYPE 2 DIABETES MELLITUS

T2DM, adult onset diabetes, is due to a decrease in insulin sensitivity. Genetic factors as well as lifestyle factors such as obesity and sedentary lifestyle are important risk factors for developing T2DM and the pathophysiological features in pancreatic beta cell failure. Beta cell failure leads to delayed and insufficient insulin secretion to stimuli, and increased insulin resistance of the liver, fat tissues and muscles. Due to physical inactivity and obesity the insulin resistance increases which leads to increased output of glucose from the liver and decreased glucose uptake in the skeletal muscles. Initially the beta cells can compensate for this with increased insulin secretion. However, over time the beta cells fail to compensate which leads to lack of insulin, hyper glycaemia and T2DM[50, 68]. Both insulin insensivity (insulin resistance) and beta cell failure also depends on genetic factors. Due to the lack of symptoms in the beginning of the disease, the diagnosis is often delayed with several years and the prevalence of 4-5 % based on register estimates in the Swedish population might be even higher due to that many patients with T2DM might go undiagnosed and without treatment [51, 69]. However, a Swedish pharmaco-epidemiological report found the prevalence

of T2DM to be 4.7% [70]. There are several medical treatments except secondary prevention with weight loss, changes in diet and physical activity, that all tries pharmacologically to get functional glucose control in different ways and today there is also treatment which shows reduction in weight loss, mortality and CVD in patients with T2DM [71-74]. However, today insulin therapy may be needed even after a short duration of T2DM[50].

The metabolic syndrome includes abdominal obesity, hypertension, impaired glucose tolerance and dyslipidemia and increases the risk of CVD and DM. The same impactful risk factors as metabolic syndrome is seen in a majority of the patients with T2DM and both the metabolic syndrome and T2DM increases worldwide[47, 74, 75]. Due to chronic hyperglycemia, microvascular- and -macrovascular complications also occur in patients with T2DM, albeit to a lesser extent then in T1DM, patients with T2DM have a shorter life expectancy compared to the general population [50, 76]. Also, smoking contributes to impaired insulin sensitivity and also increases cardiovascular disease and T2DM. At the same time, metabolic syndrome is overrepresented in other diseases, including CVD and cancer, reflecting the negative macrovascular effects of diabetes. The leading cause of death in patients with T2DM is CVD and about two-thirds of all people with T2DM, regardless of gender, die in some form of CVD and has a 2-4-fold increased risk of CVD and mortality[76-78]. Although for patients with DM the mortality in CVD has decreased the latest years as a result of earlier diagnosis, secondary prevention and advances in medical care [51, 66, 79-81]. Although these improvements, as well as post-myocardial infarction survival, is expected to increase the prevalence of chronic complications such as HF which is already overrepresented in the DM population even in the absence of ischemic heart disease (IHD)[82]. T2DM enhances the risk of HF as well as having an adverse impact on the prognosis. HF is also expected to increase in the T2DM population in the future[83]. Norhammar et al. described 90 % of comorbidities in HF patients with T2DM to be preventable [84]. IHD in these patients with T2DM have an especially negative influence on mortality, an impact that has been shown to be beneficially influenced by previous revascularization. This suggest an importance of coronary intervention in patients with T2DM and IHD. At the same time, a Swedish nationwide study described patients with AF and diabetes to have a high overall cardiovascular risk, with a higher rate of mortality and HF, exceeding those for stroke and compared to the general population. This implies that preventive treatment strategies, beyond preventing stroke with anticoagulants, are needed to be implemented in medical care for these patients[84].



1.7 CONGENITAL HEART DISEASE, TYPE 1 AND TYPE 2 DIABETES MELLITUS

During my years of medical school at Sahlgrenska Academy, Gothenburg, I entered the amanuens-program which aims to introduce students into research. I contacted professor Dellborg and

got to be a part of his research group at GUCH. After having been helping out with some research projects I asked professor Dellborg about the prevalence of DM in the ACHD population. This had to our knowledge not been studied before and we started to work on a research plan and study design on CHD and the association with DM.

Increased exposure to infections, lifestyle changes, and increased biologic stress-strain could contribute to an autoimmune response and to an increased risk of developing T1DM [85]. Patients with CHD may be more likely to be exposed to additional and more serious infections, lifestyle changes and other biological stressors or strain due to repeat diagnostics, hospitalisations, therapeutic interventions and early surgery [86-89] which could lead to an autoimmune response and therefore potentially have an increased risk of developing T1DM. The presence and development of T1DM in CHD patients have not been previously studied. We hypothesized that the coexistence of T1DM and CHD has a combined effect on individuals with both diseases, resulting in increased co-morbidity and mortality.

At the same time, patients with T2DM are overrepresented in other diseases, including cardiovascular disease, reflecting the negative macrovascular effects of diabetes. Obesity and sedentary lifestyle are important risk factors for developing T2DM, which may also be more prominent in patients with CHD than in the general population[90]. A large study, Moons et al., reported that only one in five men and women with CHD had a healthy lifestyle [90]. In addition, a relatively small study of predominantly young adults with mostly complex CHD reported that impaired glucose tolerance was prevalent in this group compared to healthy controls without CHD[91]. To our knowledge, the combined effect of CHD, including corrective surgery in childhood, and the development of T2DM on mortality and morbidity has not previously been investigated in a large reliable cohort, representing prevalence on a national level.

2 AIM

2.1 CONGENITAL HEART DISEASE, TYPE 1 AND TYPE 2 DIABETES MELLITUS – THE AIM OF THIS THESIS

The primary research aim for this thesis was to investigate whether there was an association between CHD and the risk of developing T1DM and/or T2DM in the Swedish population. The secondary aim was to investigate if there was an increased risk of mortality and morbidity in patients with CHD and DM in this cohort.

2.1.1 THE SPECIFIC AIMS OF THE STUDIES INCLUDED IN THE THESIS WERE:

Paper I, the part aim for this thesis and for paper I was to in a large national diabetes register, investigate;

- the prevalence of the combination of adult CHD and T2DM.
- describe patient characteristics, estimate the associated clinical risk, mortality and morbidity in patients with CHD and T2DM compared to patients with only T2DM.

Paper II, the part aim for this thesis and of paper II was to in a large cohort, over a longer period of time investigate;

- the results of the coexistence of T1DM and CHD on co-morbidity and mortality compared to patients with only T1DM

Paper III, the part aim for this thesis and of paper III was to in a large cohort, divided by birth cohorts, compared to the general population, over a longer period of time investigate;

- the incidence of T1DM in patients with CHD
- the mortality in patients with CHD and T1DM compared to patients with CHD and population-based controls

Paper IV, the part aim for this thesis and of paper IV was to in a large cohort, divided by birth cohort, gender and lesion of CHD cohort, compared to the general population, over a longer period of time investigate;

- the prevalence of DM in patients with CHD
- the incidence of DM in patients with CHD
- the mortality in patients with CHD and DM compared to population-based controls

3 METHOD

3.1 THE SWEDISH HEALTH CARE SYSTEM AND PERSONAL IDENTITY NUMBER

All Swedish citizens are provided with a unique 10-digit (currently 12 digit) personal identity number (PIN). The PIN system was introduced in 1947 and is based on date of birth, sex, and until 1990 region of birth. The number of people residing in Sweden missing a PIN was calculated to be 0.6% in 2006[92]. The PIN system enables each person to be followed over time and across registers of data.

The health care system and all hospitals in Sweden are publicly financed and offer care at low cost to all Swedish adult citizens and free to children. This enables all Swedish citizens to access equal medical care.

This is of importance for the methodology of this thesis as this approach is mandatory and enables all citizens to be included in national health care registers in Sweden, compared to many international settings where epidemiological research is conducted on specific insurance registers linked to an insurance number, not being mandatory, excluding patients without an insurance plan and number as well as those patients who do not want to be a part of the register. In Sweden, researchers can use the PIN-system to link different registers, which gives large, reliable, powerful health care registers making a good base for epidemiological research. The National Board of Health and Welfare in Sweden administer the health care registers which are mandatory for all inpatients and outpatients and is automatically registered for all patients. The population based registers are administrated by Statistics Sweden. Other national quality registers managed by other national register holders are not mandatory for the healthcare to report to and is based on individual informed consent. However, most patients and caregivers participate voluntarily and these quality registers are also trustworthy with good coverage.

3.2 EPIDEMIOLOGY RESEARCH, REGISTERS AND CONSIDERATION OF STUDY DESIGN FOR PAPERS I-IV

When choosing study design, one must have in mind the null hypothesis (H0). The H0 in this thesis and in papers I-IV was that CHD does not affect the risk of being diagnosed with DM, or of mortality and diabetes related morbidity. To prove the opposite and to demonstrate the hypothesis (H1) an epidemiological, observational and analytical study was considered appropriate. In this case only a retrospective study was reasonable, since large time periods would be required to study the outcomes of DM onset and mortality. The two optional study designs that were considered were case-control studies and cohort studies (Fig 4). However, for paper I-IV, a cohort study design was considered appropriate. Papers I-II of this thesis lacked a control group without DM, and only DM patients with and without CHD were compared over time. This type of study design,

dependent on that register data including only specific disease populations were used, are somewhat more difficult to categorize. We have for simplicity chosen to name the patient categories as cases and controls, but in a true scientific sense, these studies can rather be categorized as retrospective cohort studies within T1DM/T2DM populations with CHD and non-CHD as exposure cohorts with mortality and non-mortality as the outcomes. Papers III-IV are also to be categorized as retrospective cohort studies, but in these study designs with CHD and non-CHD as exposure cohorts with T1DM/T2DM and non-T1DM/T2DM as the outcomes. The advantage of using a cohort study design as described is that the incidence rate, odds ratio and relative risk can be calculated for each cohort and it can be compared to the background population and compared to

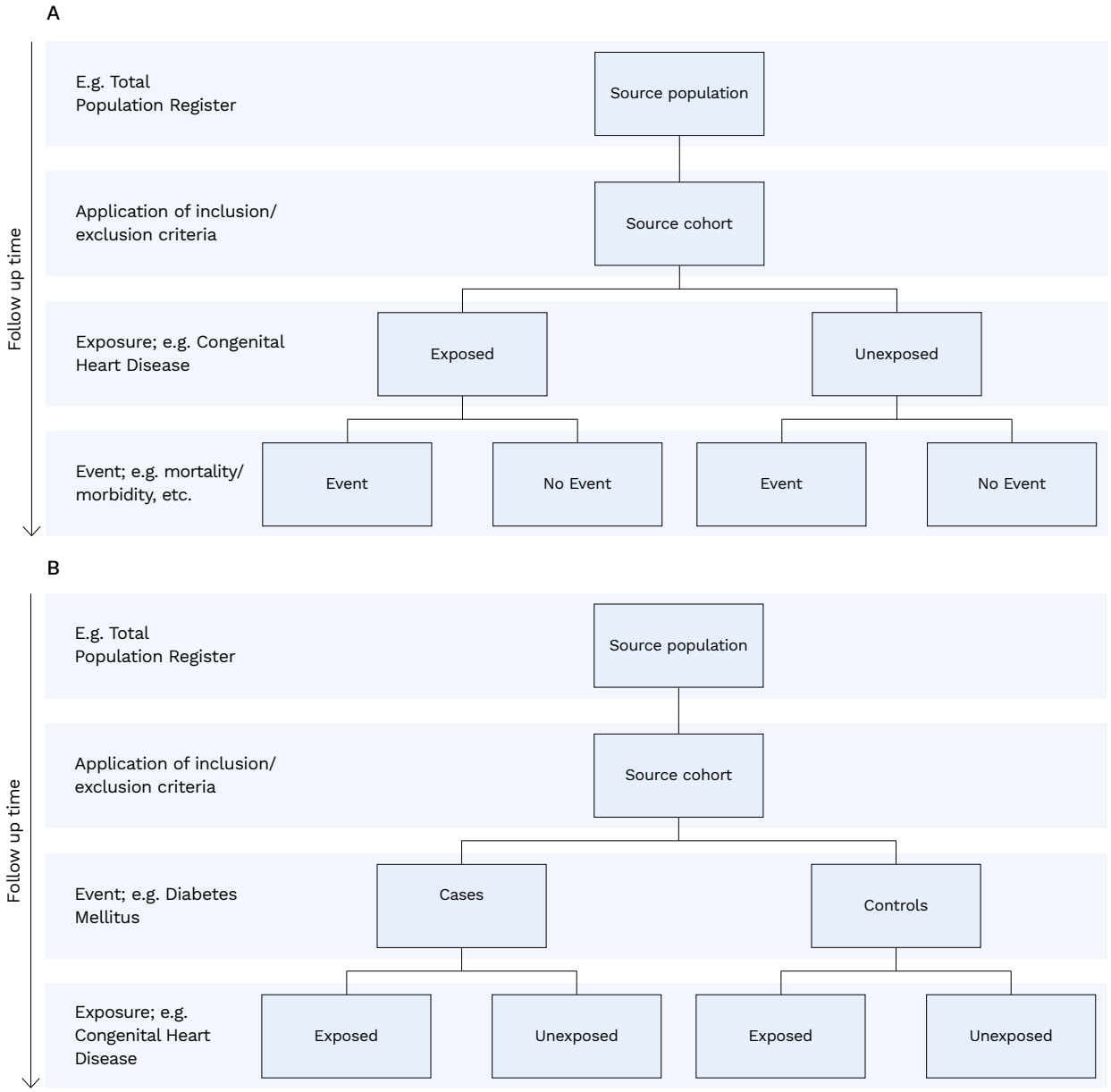


FIGURE 4. A, B. Illustration of a cohort study design (A) and a case control study design (B).

other studies. Whereas case-controls studies only provide estimate of a ratio measurement of effect (odds ratio). A cross sectional study can describe the prevalence.

The method used in this thesis and the papers it is built of rely on epidemiologic retrospective analytic cohort studies. Ideally the cohorts should be as similar as possible, with exception of the exposure factor (in this case CHD) so that the outcome(s) can be compared with limited confounding. The exposed and unexposed groups in the current papers were matched, which refers to selection of controls to be as similar as the cases. Often used matching criteria are true confounding variables such as gender and age. If matching criteria has not been chosen wisely and not true confounding variables are used for matching, bias can instead be introduced into the study[2]. To be able to collect cohorts for these studies national health care registers were used.

Patients with CHD are diagnosed in standardized clinical practice and through clinical consensus by licensed physicians. Patients with DM are diagnosed in standardized clinical practice by blood sample and clinical consensus, described in the introduction, and followed by licensed physicians.

3.2.1 THE SWEDISH NATIONAL PATIENT REGISTER

The Swedish National Patient Register (NPR) was started in 1964 and includes statistics of all diagnoses, diseases, hospitalizations, and surgical treatment of all Swedish citizens coded by ICD-codes. From 1987, the NPR included all in-patient care, including principal and contributory discharge diagnoses, and surgical procedures, in Sweden. From 2001, the NPR also includes information on diagnosis in non-primary outpatient care, including outpatient hospital visits, day surgery and psychiatric care from private and public caregivers coded according to ICD-10. Today NPR is often divided by the Inpatient Register and the Outpatient register. The NPR is updated once a year and includes information on patient data, geographical data, administrative data, and medical data. NPR is considered to be highly reliable because it includes all Swedish citizens and the PIN enables each individual to be followed over time. The NPR includes mandatory information on all primary and secondary discharge diagnoses, which are classified according to the International Classification of Diseases (ICD). From 1961, patients are also being reported as alive or deceased when discharged and this is reported in the Swedish Cause of Death Register (CDR) [93]. The six cardiothoracic surgery clinics in Sweden have registered all procedures and hospitalizations since 1970.

3.2.2 THE SWEDISH NATIONAL DIABETES REGISTER

In 1996 the Swedish National Diabetes Register (NDR) was established as a tool for quality improvement in the care of adult patients with diabetes, managed by the Centre of Registers in Region Västra Götaland, Gothenburg, Sweden [94]. NDR currently includes data from more than 720.000 adult patients (1996-2019), including 448 477 living patients, based on data obtained by informed consent, with T1DM or T2DM[51, 66]. More than 90% of Swedish adult patients with DM are included in the NDR containing high quality data with high level of detail [51]. When the NDR was established, register data were collected from hospitals and primary healthcare centers. Children with diabetes are registered in SWEDIABKIDS and data are transferred to the NDR at 18 years of age. Annual reporting to the NDR is based on information that is collected during

patients' visits to hospitals and primary healthcare centers nationwide at least once yearly. The register contains data on primary (T2DM), outpatient (mostly T1DM) and inpatient (mostly T1DM) -care, demographics, duration of diabetes, treatment modalities, cardiovascular risk factors, and associated complications of diabetes [51, 95].

3.2.3 CAUSE OF DEATH REGISTER

The Cause of death Register (CDR), is a nationwide register, containing all deaths that occurred in Sweden from 1961 but there is also a historical CDR for the years 1952–1960. Until 2011, the register included only deceased persons who were registered in Sweden at the time of the death, independently of if the death occurred in Sweden or abroad. From 2012, deaths that occur in Sweden are also included where the person was not registered in Sweden at the time of the death. These deaths are included in the register just over a year after other deaths. However, stillbirths are not included in the register[96].

3.2.4 THE REGISTER OF TOTAL POPULATION

The Register of Total Population (RTP) was started in 1968 and is the basic registration of the population in Sweden and is available from Statistics Sweden. The register is an excerpt from the Census Register for which the Swedish Tax Agency is responsible. The RTP is primarily used as a base register for the production of statistics on population size and composition and is often used as background information in medical and behavioral science research. The register includes variables on PIN, name, gender, birthplace, address, residency, civil status, economy, immigration and emigration. The coverage is trusted to be almost complete and is updated once a month[97].

3.2.5 THE SWEDISH REGISTER OF CONGENITAL HEART DISEASE

The Swedish Register of Congenital Heart Disease (SWEDCON) is an extension of the previous GUCH (Grown Ups Congenital Heart Disease) register, a quality register started in 1998 including both children and adults with CHD. This register, based on individual patient data obtained by informed consent, held by Uppsala Clinical Research Center, contains high quality data with high level of detail, but based on a more limited portion of the CHD population and this is why it was chosen not to be used in this thesis. However, SWEDCON also includes data on surgical and catheter-borne treatment of congenital heart disease. The purpose of the register is to be able to monitor patients from childhood up to adulthood and thus obtain as complete information as possible about the natural course and treatment results for various congenital heart malformations. Data

TABLE 6. Registers used in this thesis, paper I-IV.

	Register				
Paper	RTP	NPR	NDR	CDR	SWEDCON
I	X	X	X	X	X
II	X	X	X	X	X
III	X	X		X	
IV	X	X		X	

RTP= Register of Total Population, NPR= National Patient Register, NDR= National Diabetes Registry, CDR= Cause of Death Register, SWEDCON= Swedish Cogenital Heart Disease Registry

from local pediatric cardiology registers have been incorporated as well as data from the pediatric cardiac surgery section of the Swedish Cardiac Surgery Register[98].

3.3 STRENGTHENING THE REPORTING OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY

To be able to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) a specific international checklist has been initiated as a collaboration between epidemiologists, methodologists, statisticians, researchers and journal editors. This checklist is considered representative of highest methodologic quality to be used, when applicable, when conducting epidemiologic research (Appendix A)[99]. The STROBE checklist has been used when applicable in this thesis.

3.4 DISEASE CLASSIFICATION

To be able to epidemiologically define diagnosis in registers, a widely accepted standard for disease classification for all clinical and research purposes, published by the WHO, the International Statistical Classification of Diseases and Related Health Problems (ICD), were used when applicable[100]. The primary purpose of the ICD, which is about 100 years old, is to enable the classification and statistical description of diseases including morbidity and mortality. WHO has been administrating and been responsible for the ICD since 1948. The ICD has been revised and published in several additions to reflect advances in health and medical science since it started. The 10th edition of ICD (ICD-10) was introduced in 1990 and it is cited in more than 20,000 scientific articles and used by more than 100 countries around the world[100]. The Swedish version of ICD-10 is called International Statistical Classification of Diseases and Related Health Problems - Systematic List (ICD-10-SE). The classification is mandatory for reporting to the National Board of Health's health data register[101]. For this thesis, the 8th edition of ICD (ICD-8) was used from 1968 to 1986, the 9th edition (ICD-9) from 1987 to 1996, and the 10th (ICD-10) edition of ICD from 1996 onwards (Appendix B) [102]. Still, the translation between the different editions of ICD is not coherent and in complicated cases were a CHD diagnosis is not fully coherent with the CHD groups chosen for the study, the patient has in the analyses been categorized to the more severe ICD classification.

3.5 THE METHOD OF PAPER I-IV

3.5.1 PAPER I

3.5.1.1 STUDY DESIGN

In paper I, a nationwide retrospective register based comparative cohort study was performed. The H0 for paper I was that there was no difference in prevalence of T2DM in the adult CHD population compared to the general population, and no difference in morbidity or mortality in patients with CHD and T2DM compared to patients with only T2DM.

To be able to describe the prevalence of CHD and T2DM an estimate was done. The exact number of adult patients with CHD in Sweden was not known at the time. Therefore we estimated the number of CHD patients in Sweden using the nationwide SWEDCON quality register that includes adult patients with CHD[103]. To put the estimated Swedish prevalence in relation to international

data, the prevalence estimate was compared to a population-based estimate from Quebec[25].

Further, the study challenged the H0 and described the estimated prevalence of CHD in the T2DM population as well as the morbidity and mortality in patients with CHD (exposed) in combination with T2DM compared to control patients with only T2DM (unexposed) matched for sex, year of birth and year of first entry into the NDR with T2DM but no CHD. The cohort was followed from entry into NDR until death or 31 June 2012. Information on date and cause of death were collected from CDR.

3.5.1.2 STUDY POPULATION

CHD diagnoses were defined according to the 9th edition of ICD (ICD-9), codes 745–747 (first 3 numbers available) and 10th edition of ICD (ICD-10) codes Q20–28 (first 2 numbers available). Other ICD 10 codes used, for morbidity registration, were I50 for heart failure, I48 for atrial fibrillation, and I20, I22, I24.8, I24.9 and I25 for ischemic heart disease (Appendix B).

To include almost all patients with DM in Sweden, the NDR was used. Patients with T2DM were distinguished from patients with T1DM in the register based on T2DM being defined with the following inclusion criteria:

- in epidemiological terms (DM ICD diagnosis code),
- namely (DM), and either
    - treatment with diet only,
    - or treatment with oral hypoglycemic agents only,
    - or onset age of diabetes >40 years and treatment with insulin only or in combination with oral agents.

This to avoid systematic errors as misdiagnosing and misreporting to the register because it is clinically unlikely to develop T2DM before 40 years of age as well as not having a treatment when being diagnosed with T2DM.

To be able to collect data individually, all data from the NDR were linked with the NPR and the Swedish CDR by the PIN. By NDR and NPR, a control group of patients with DM but without CHD were identified and out of this cohort, with the inclusion criteria above, patients with T2DM were identified. By using the ICD codes for the CHD diagnosis in NPR patients with CHD and T2DM could then be identified in the NDR. The identifying was done by the PIN and a specific coded identification number linked to the PIN. To achieve matched controls at a ratio of 1:5 and match for confounders, the patients identified in the NDR with CHD and T2DM were matched with patients out of the control cohort for sex, year of birth and year of first entry into the NDR. To achieve the final study population, the exclusion criteria for the patients in the study were:

- unknown duration of diabetes
- body mass index (BMI) below 18.5 or above 45 kg/m2
- creatinine less than 20 micromoles/l or more than 800 micromoles/l.

This resulted in the final study population, as shown in figure 5.

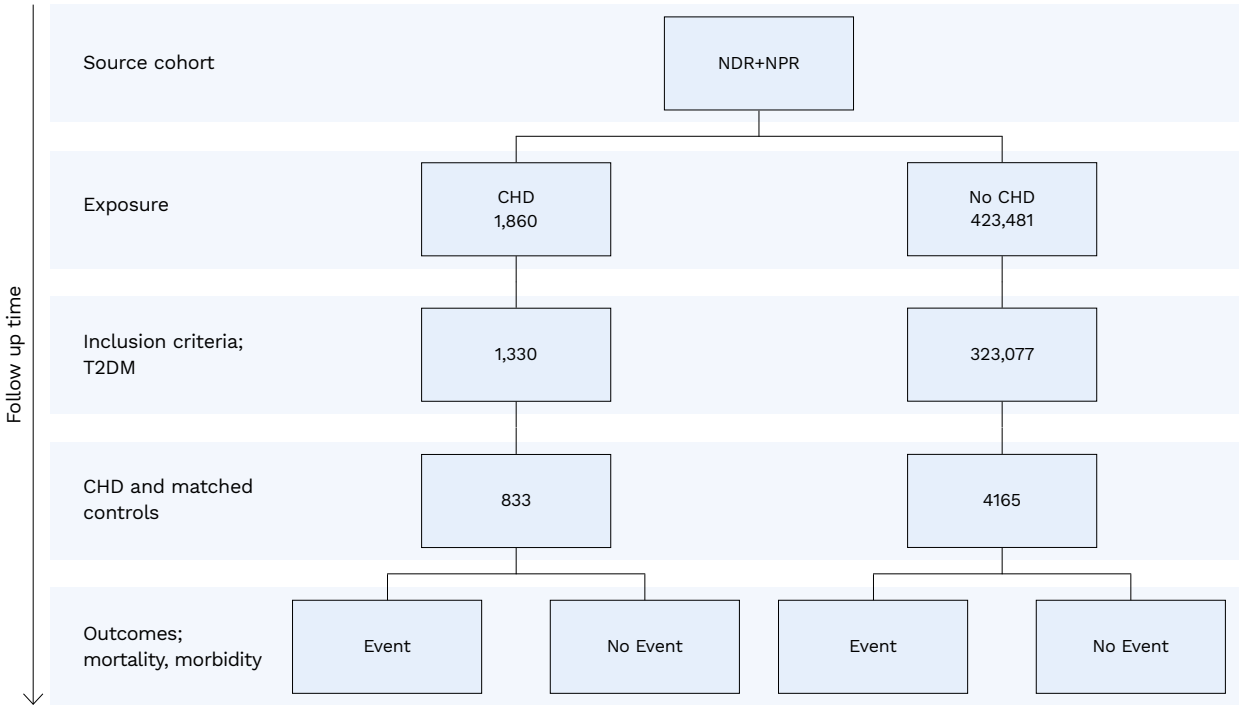


FIGURE 5. Retrospective cohort design study in paper I. There were 425,375 individuals in the National Patient Register (NPR) and 541,038 adults in the National Diabetes Register (NDR). By merging NPR with NDR, 423,481 diabetes diagnoses could be found in this 83-year period. A total of 323,077 were unique individuals with type 2 diabetes mellitus, sorted by national personal identity number and given individual patient IDs. 1,860 unique patients with diabetes mellitus (type 1 or type 2) and congenital heart disease could be identified, of them 1,330 patients with congenital heart disease and type 2 diabetes were found. After exclusions and matching criteria, a total of 833 patients with congenital heart disease and type 2 diabetes were included in the study, matched to 4,165 patients with only type 2 diabetes but no congenital heart disease. DM= Diabetes Mellitus, T2DM= Type 2 Diabetes Mellitus, CHD=Congenital Heart Disease.

All patients in the NDR are above 18 years of age on entry in the register and by matching the unique PIN of all adult patients in the NDR to the NPR, information was collected about adult patients with CHD. To challenge the H0 about the outcome of morbidity, information was retrieved about morbidity from the NPR on hospitalizations for congenital heart disease, events of ischemic heart disease, heart failure, atrial fibrillation, stroke, percutaneous coronary intervention, coronary artery bypass grafting, renal failure and cardiovascular death.

3.5.1.3 STATISTICAL ANALYSIS

In paper I, normally distributed data was presented as mean (standard deviation) and non-parametric data are presented as median (interquartile range, IQR). Tests for trend in proportions were conducted using non-parametric tests: the Kruskal–Wallis one-way analysis of variance for continuous data and the chi-square test for nominal data.

A logistic regression model was used for estimation of odds ratios, and 95% confidence intervals

are presented for characteristics and cardiovascular events.

The log-rank test and Kaplan–Meier estimator were used for the survival analysis of time since onset of diabetes. A two-tailed P value less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3.5.2 PAPER II

3.5.2.1 STUDY DESIGN

Paper II, was designed as a nationwide retrospective register based comparative cohort study. The H0 for paper II was that the coexistence of T1DM and CHD does not result in a difference in co-morbidity or mortality compared to patients with only T1DM. The study challenged the H0 and described the morbidity and mortality in patients with CHD (exposed) in combination with T1DM compared to control patients with only T1DM (unexposed). The two groups were matched to avoid confounding for sex, year of birth and year of first entry into the NDR. To be able to describe the prevalence of CHD and T1DM, a post-hoc estimation of prevalence was done as a cross sectional study in this thesis. The exact number of adults with CHD in Sweden were at this time not known, therefore the estimated numbers of CHD patients in Sweden were based on the nationwide SWEDCON quality register. To put the estimated Swedish prevalence in relation to international data, the prevalence estimate was compared to a population-based estimate from Quebec[25].

The number of Swedish CHD patients with T1DM, was collected by using the NDR. The two groups (exposed and unexposed) were matched to avoid confounding, for gender, year of birth and year of first entry into the register. Patients were followed from entry into the register until death or 31 June 2012. Information on date and cause of death was collected from CDR.

3.5.2.2 STUDY POPULATION

The same research methodology as in paper I was used for paper II except for the definition of T1DM. By using the ICD codes for the CHD diagnosis, patients with CHD were identified in the NPR (Appendix B). To be able to retrieve data individually, all data from the NDR were linked with the NPR and the Swedish CDR by the PIN. To be able to define patients with T1DM and to distinguish patients with T1DM from those with T2DM and avoiding systematic errors as incorrectly recorded data in the NDR, T1DM was defined in epidemiological terms (ICD code) and by inclusion criteria of:

- treatment with insulin only or in combination with oral hypoglycemic agents
- and onset age of DM ≤30 years.

Exclusion criteria were;

- unknown duration of diabetes
- diagnosed with T1DM but had no insulin treatment
- body mass index <18.5 or >45 kg/m2
- glycosylated hemoglobin (HbA1c) levels <25 or >135 mmol/mol
- systolic blood pressure <80 or >236 mmHg
- Patients who had migrated from Sweden

By NDR and NPR, a cohort of potential control patients with DM but without CHD were identified and based on the inclusion and exclusion criteria above patients with T1DM were further selected.

To achieve matched controls at a ratio of 1:5, the patients identified in the NDR with CHD and T1DM were matched for sex, year of birth, and year of first entry into the NDR. This came down to the final study cohort, Fig. 6.

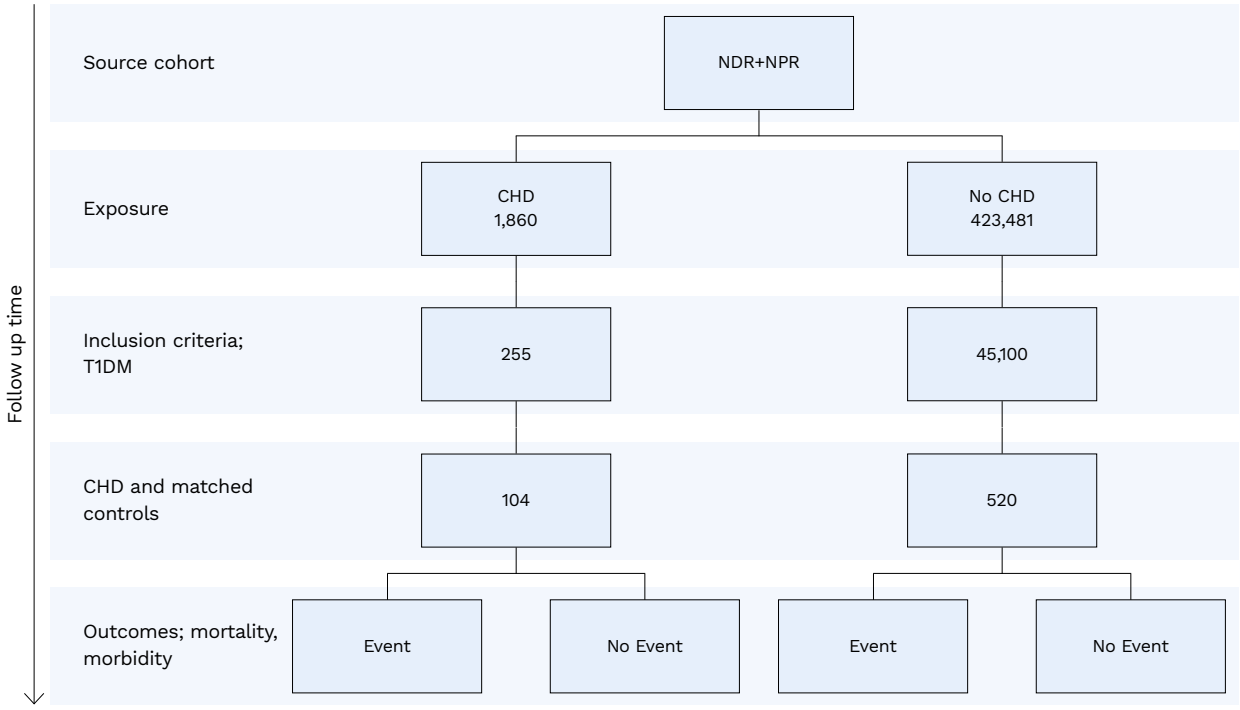


FIGURE 6. Retrospective cohort design study in paper II. There were 425,375 individuals in the National Patient Register (NPR) and 541,038 adults in the National Diabetes Register (NDR). By merging NPR with NDR, 423,481 diabetes diagnoses could be found in this 83-year period. A total of 45,100 were unique individuals with type 1 diabetes mellitus, sorted by national personal identity number and given individual patient IDs. 1860 unique patients with diabetes mellitus (type 1 or type 2) and congenital heart disease could be identified, of them 255 patients with congenital heart disease and type 1 diabetes were found. After exclusions and matching criteria, a total of 104 patients with congenital heart disease and type 1 diabetes were included in the study, matched to 520 patients with only type 1 diabetes but no congenital heart disease. DM= Diabetes Mellitus, T1DM= Type 1 Diabetes Mellitus, CHD=Congenital Heart Disease.

All patients in the NDR are above 18 years of age on entry in the register and by matching the unique PIN of all adult patients in the NDR to the NPR, information was collected about adult patients with CHD. To challenge the H0 about co-morbidity, information was retrieved about morbidity from the NPR on hospitalizations for CHD, history of ischemic heart disease, heart failure, atrial fibrillation, stroke, percutaneous coronary intervention, coronary artery bypass grafting, renal failure and cardiovascular death was retrieved from the NPR. Information on date and cause of death was collected from the CDR.

3.5.2.3 STATISTICAL ANALYSIS

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA), MedCalc® (MedCalc Software bvba, Ostend, Belgium), and Microsoft Office Excel 2007, 2010 (Microsoft AB, Kista, Sweden). To challenge the H0 of the paper a two-tailed t-test with a p value <0.05 for paired data, was considered statistically significant. Data were shown as mean values for continuous variables, and as percentages for categorical variables.

3.5.3 PAPER III.

3.5.3.1 STUDY DESIGN

In paper III, we performed a retrospective register based comparative cohort study. The H0 for paper III was that there was no difference in incidence of T1DM or mortality in patients with CHD compared to general population-based controls. To challenge the H0, the study described the incidence of T1DM and the mortality in adult patients with CHD, with or without onset of T1DM, compared to a population-based control cohort without CHD, with or without onset of T1DM. To avoid confounders the CHD cohort and the control cohort was matched by gender, year of birth and county of birth. The cohort was divided by year of birth, all (1970-1993), first birth cohort (1970-1984), and second birth cohort (1985-1993) and followed from birth until death or December 31 2011, a maximum of 42 years. To be able to describe the prevalence of CHD and T1DM, a post-hoc estimation of prevalence was done as a cross sectional study in this thesis.

For paper III, all data were obtained from the NPR, including Inpatient and Outpatient register, and CDR linked through the PIN.

3.5.3.2 STUDY POPULATION

All discharge and hospital outpatient visit diagnoses were coded according to the ICD system (ICD8-10). CHD was epidemiologically defined according to the ICD-8 codes 745-747, ICD-9 codes 745-747 and ICD-10 codes Q20–25 and by at least one outpatient visit, hospitalisation, or death certificate due to CHD ICD code (Appendix B). All men and women who had a diagnosis of CHD registered in the Inpatient, Outpatient, or CDR, and were born between January 1970 and December 1993 were included in the cohort. Follow-up data and mortality were collected from 1970 until December 2011.

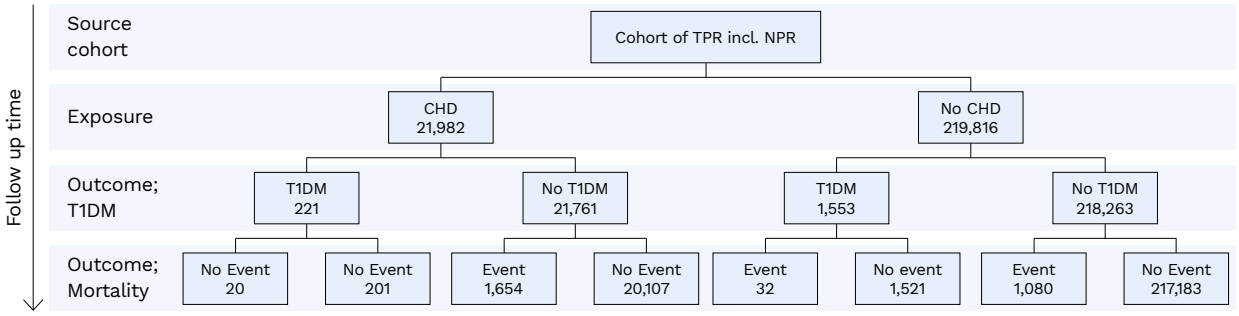
Patients were included in the study at the date of their first registration with a diagnosis of CHD in the NPR. The hierarchic classification was used for CHD stratification as described by Liu and modified by Botto [26, 27] (table 5), consisting of conotruncal defects (lesion group 1), nonconotruncal defects (lesion group 2), coarctation of the aortae (lesion group 3), ventricular septal defect (lesion group 4), atrial septal defect (lesion group 5) and other heart and circulatory system anomalies (lesion group 6). Each CHD patient was matched with 10 population-based control individuals, without a

diagnosis of CHD, and were randomly selected from the RTP in Sweden, matched by year of birth, sex, and county. However, a total of 14 patients in the cohort could only be matched by 9 controls each. The CHD and control cohorts were followed regarding diagnosis of T1DM in the NPR, until death or until the end of the study, December 31, 2011.

DM was epidemiologically defined as codes 250 (ICD8 and ICD-9) or E10-14(ICD-10). To distinguish patients with T1DM from those with T2DM in the NPR and to adjust for systematic errors and overestimation of T1DM in the NPR, T1DM was defined as follows in the investigation:

- Diagnosis of DM
- Onset age of DM ≤26

This came down to the final study population (Fig. 7).



CHD: Congenital Heart Disease, NPR: National Patient Register, RTP: Register of Total Population, T1DM: Type 1 Diabetes Mellitus

FIGURE 7. Retrospective cohort study design in paper III. All adults, born between January 1970 and December 1993, who had a Congenital Heart Disease diagnosis in the National Patient Register were included in the cohort (n=21,982). Each patient with Congenital Heart Disease, was matched with 10 population-based, randomly selected controls from the Total Population Register in Sweden controls, matched by year of birth, sex, and county. Patients with Congenital Heart Disease were followed regarding diagnosis of T1DM (n=221) in the NPR until death (n=20) or until the end of the study (n=201). Follow-up data and mortality were collected from 1970 until December 2011.

Data was linked between the NPR and the Swedish CDR by the PIN and information on date and cause of death was collected from the CDR.

3.5.3.3 STATISTICAL ANALYSIS

Baseline characteristics are presented as numbers and proportions for each lesion type by CHD patients and controls separately. For continuous variables the mean follow-up time and standard deviation was reported. A chi-square test for categorical variables was used to compare the prevalence between cases and controls and t-test was used for continuous variables. A p-value of <0.05 was considered as statistically significant. Incidence rate with 95% confidence interval (CI) of T1DM and mortality were calculated as per 10,000-person-years and reported separately by birth-cohorts (1970-1993, 1970-1984 and 1985-1993).

To investigate how the diabetes diagnosis among patients with CHD and controls effect the mortality, a multi-state model based on the principal of Markov model was used. The diabetes model consisted of three different health states; CHD, T1DM and death as absorbing state (Fig. 8). A transition from one health state to another occurs by an event, T1DM or death.

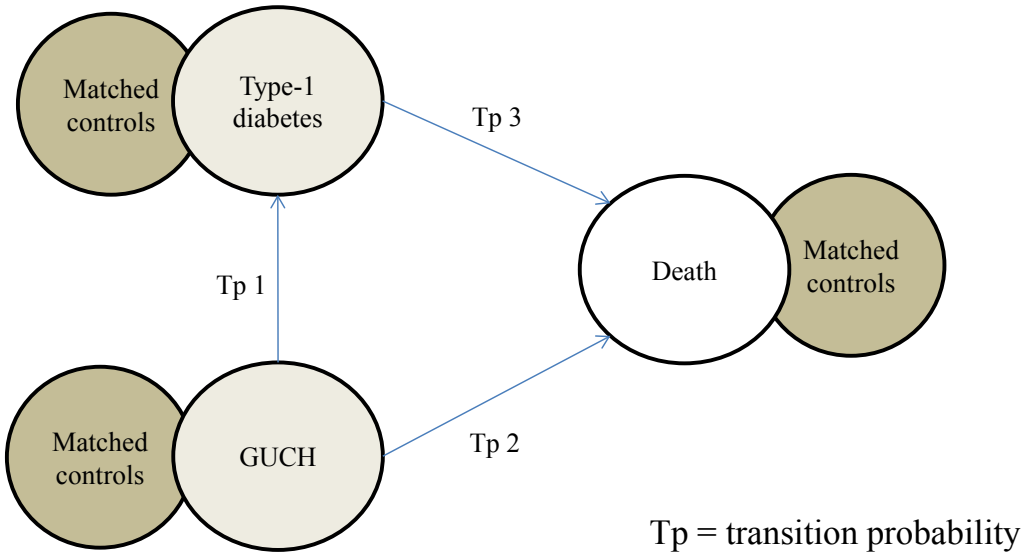


FIGURE 8. The Markow model used in paper III. The diabetes model consisted of three different health states; Congenital Heart Disease (CHD), Type 1 Diabetes Mellitus (T1DM) and death as absorbing state. A transition from one health state to another occurs by an event, T1DM or death.

The follow-up time was until first occurrence of hospitalization due to T1DM, death or end of study (31 December 2011) for all patients with CHD and controls. In the Cox multistate regression model the matching has at baseline been done by sex, date of birth and county of birth. Over time they diverse and over time as the patients receive T1DM they are compared separately. Although the matching for gender remain unmodified through the whole multistate. For each transition a Cox proportional regression model was used to estimate the relative risk of T1DM and death among patients with CHD versus controls, yielding a hazard ratio (HR) with 95% CI (reported separately by birth-cohorts). To test the proportionality for each model a visual assessment based on Schoenfeld residuals was performed.

Due to the unequal distributed numbers of the CHD population and to achieve proportionality in the model, a post-hoc analysis follow-up time was divided up into intervals (0-4, 5-9, 10-17 and 18+ years) to be analyzed in the multistate

model. This was done for the whole cohort and each birth cohort, separately.

All statistical analyses and data processing were performed with R software, Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria)[104]. The "mstate" package was used to fit the multi-state model.

3.5.4 PAPER IV.

3.5.4.1 STUDY DESIGN

In paper IV, we performed a retrospective register based comparative cohort study. The H0 for paper IV was that there was no difference in prevalence of adult onset DM, incidence of adult onset of DM or mortality in patients with CHD compared to general population-based controls. To challenge the H0, the study described the prevalence and first-onset incidence of DM, morbidity and the mortality in adult patients with CHD after 35 years of age before and after onset of DM divided by birth cohort, (first birth cohort born 1930-1959, second birth cohort born1960-1983 and all cohort born 1930-1983), gender cohort and lesion of CHD cohort. For every patient with CHD, 10 controls from the general population without CHD-diagnosis were matched for sex and year of birth, with a follow-up from birth until 2017, a maximum of 87 years (1930-2017).

3.5.4.2 STUDY POPULATION

The same research methodology was used for paper IV as in paper III except for the definition of DM and the follow up time. All men and women born between January 1930 and December 1983 who had a diagnosis of CHD and were registered in the Inpatient, Outpatient, or Cause-of-Death Register were included in the cohort. Follow-up data and comorbidities were collected until December 2017. The hierarchic classification was used for CHD stratification as described by Liu and modified by Botto [26, 27] (table 5).

All men and women born between January 1930 and December 1983 who had a diagnosis of DM and were registered in the Inpatient, Outpatient, or Cause-of-Death Register were identified within the cohort. Diabetes mellitus was defined as codes 250 (ICD-8 and ICD-9), or E10-14(ICD-10). To include only first-onset of adult onset DM in NPR, patients were included in the current study if they had;

- diagnosis of DM according to ICD8-10
- onset age of DM ≥35 years

Exclusion criteria for the patients in the cohort were;

- death <35 years of age
- diagnosis of DM after death

This came down to the final study population (Fig. 1, Papers, paper IV).

Data was linked between the NPR and the Swedish Cause of Death Register by the PIN. Information on date and cause of death was collected from the Cause of Death Register. All diagnosis codes used in the current study is found in Appendix B.

To challenge the H0 and to compare the mortality and morbidity after DM, both patients with CHD and controls were studied after onset of DM.

3.5.4.3 STATISTICAL ANALYSIS

For details regarding method and statistical analysis, see Papers, paper IV.

4 ETHICS

The purpose of ethics in medical research is to protect the individual. The balance between risks to the individual and knowledge gains are two factors that always should be considered in studies. Also, in epidemiological research one must have in mind that new risk information about a specific population can also lead to concern in this group even if the purpose of the study is ultimately to prevent risks in the population.

An approval from a Regional Ethics Review Board in Sweden must be in place before research can be initiated on data in Swedish medical registers[105].

In paper I and II, all included patients agreed by informed consent to be registered in the NDR before inclusion in the study. For these studies the patient names were excluded from the dataset and the PIN for each patient in the NDR was linked and replaced with a code key by the register.

The computations for paper III and IV, were based on individual data from the Swedish registers, RTP and NPR, held by the National Board of Health and Welfare. All personal data are subjected to secrecy in accordance with the Swedish Public Access to Information and Secrecy Act (OSL, 2009:400). The data used are available to researchers on request to the National Board of Health and Welfare pending approval by the appropriate ethics committee [106], and the Board can also provide information about the register and persons to contact for queries. For these studies the patient names were excluded from the dataset and the PIN for each patient in the NPR was linked and replaced with a code key in the final data set by the National Board of Health and Welfare of Sweden, and informed consent for these studies study could not be provided considering the study set ups and was therefore waived.

For the four studies, the study protocols conform to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approvals by the Regional Ethical Review Board in Gothenburg, Sweden.

All relevant aggregated data on number of cases and controls are contained within the thesis, its supporting information files, and its supporting information.

5 RESULTS

5.1 PAPER I

5.1.1 THE BASELINE CHARACTERISTICS

In paper I, a total of 423,481 adult individuals with DM (T1DM or T2DM) but without CHD were identified from NDR and NPR. From NDR and NPR, 1,860 adults were identified with both DM and CHD. Out of those patients with both DM and CHD, 1,330 individuals with T2DM and known year of onset of T2DM were included in the study. Among patients with T2DM but without CHD in the NDR, 323,077 patients with known year of onset of T2DM were included in the study. After inclusions and exclusions criteria, as described in the method section, a final study population of 833 patients with CHD and T2DM in the CHD cohort, was compared with 4,165 matched controls with T2DM but without CHD in the control cohort (Fig. 5). Almost half the patients (49.8%), with CHD and T2DM, consisted of patients with transposition of the great arteries, tetralogy of Fallot, atrial and ventricular septal defects (745, Q20, Q21) and 23% of patients had coarctation of the aorta code as primary CHD diagnosis (747, Q25).

5.1.2 THE PREVALENCE OF T2DM

The number of Swedish CHD patients with T2DM, as determined in the cohort of this study, was 1,330. Based on the SWEDCON quality register data, the number of adult patients with CHD was estimated to be 17,436. The estimated prevalence of T2DM by using these data was 7.6% among CHD patients (i.e. 1,330/17,436). To put this in relation to international data, applying a population-based estimate from Canada with a CHD prevalence of 0.4% on the adult population in Sweden, this estimate would instead indicate that there are 32,000 adult patients with CHD in Sweden. The prevalence of T2DM could then be estimated to be 4.2% among Swedish patients with CHD compared with the estimated prevalence of 4.2 % (323,077/7,627,772) in patients with T2DM without CHD in Sweden 2012.

5.1.3 THE MORTALITY AND MORBIDITY

The characteristics of adult patients with CHD and T2DM compared to patients with only T2DM and the data at the last registration in the NDR register, are presented in table 6. CHD patients had a slightly but nominally significantly shorter duration of T2DM compared to patients with only T2DM (7 years vs. 8 years, $P<0.05$, table 7), had a significantly lower BMI, higher creatinine and a trend ($P= 0.059$) towards somewhat lower systolic blood pressure.

As described in paper I, sedentary lifestyle was more prominent in patients with CHD and T2DM compared to patients with only T2DM and 39.5% reported were to participate in physical activity never or less than once a week compared to 33.3% of patients with only T2DM ($P=0.002$, Table 8). However, CHD patients with T2DM were less often smokers compared

to patients with only T2DM (10.7% vs. 14.1%, P=0.01). Although the medical treatment of diabetes, hypertension and lipids, were similar in the two groups (Table 8), there was a significant difference in use of aspirin. Aspirin was given to 45.9% of the patients with only T2DM compared to 41.8% of patients with T2DM and CHD (P=0.04).

TABLE 7. Characteristics of CHD patients with T2DM and patients with T2DM only (continuous variables).

Last registration†	CHD + T2DM (n = 833)	T2DM (n = 4165)	P value
	median (interquartile range) (n)	median (interquartile range) (n)	
Age in years	70 (62–78) (833)	70 (62–78) (4165)	0.3
Diabetes duration, years	7(4–11,5) (833)	8 (4–12) (4165)	<0.05
Waist measurement, cm	102 (94–112) (526)	102 (95–112) (2858)	0.6
BMI, kg/m2	28.4 (25.2–31.9) (788)	28.8 (25.9–32.4) (3982)	0.01
Systolic blood pressure, mm Hg	133 (125–145) (823)	135 (125–145) (4107)	0.06
HbA1c (IFCC), mmol/mol	51 (45–61) (823)	52 (52–65) (4165)	0.3
Creatinine, µmol/l	78 (66–97) (767)	77 (66–93) (3885)	0.04

Group comparisons were conducted using nonparametric tests: Kruskal–Wallis one-way analysis of variance for continuous data and chi-square test for nominal data.†The last registration date is 30 June 2012.

CHD + T2DM: Congenital Heart Disease and Type 2 Diabetes Mellitus, Control: Patients with T2DM only, BMI: Body Mass Index, HbA1c: glycosylated haemoglobin A1c. Data presented as median (IQR) and n (%).

TABLE 8. Characteristics of CHD patients with T2DM and patients with T2DM only at last visit.

Characteristic	CHD + T2DM % (n)	T2DM % (n)	OR*(95% CI**), P value
Previous hospitalisation^	14 (833)	10 (4165)	1.48 (1.19,1.85), 0.001
Smoker	11 (819)	14 (4097)	0.74 (0.58,0.93), 0.001
Microalbuminuria	28 (717)	25 (3677)	1.49 (0.96,1.37), 0.1
Antihypertensive agents	82 (824)	79 (4110)	1.18 (0.97,1.43), 0.09
Lipid-lowering agents	58 (806)	59 (4067)	0.98 (0.84,1.14), 0.8
Acetylsalicylic acid, aspirin	42 (763)	46 (3935)	0.85 (0.72,0.99), 0.04
Diet only	23 (833)	23 (4162)	1.01 (0.84,1.20), 1
OHA*** only	44 (833)	44 (4162)	0.97 (0.84,1.13), 0.7
OHA and insulin	17 (833)	18 (4162)	0.93 (0.76,1.13), 0.4
Insulin only	16 (833)	15 (4162)	1.13 (0.92,1.38), 0.2
Physical activity (self-reported)			
Never or < 1 times/week	40 (678)	33 (3636)	1.31 (1.11,1.57), 0.002
Regular 1–2 times/week	19 (678)	22 (3636)	0.83 (0.68,1.03), 0.09
Regular > 3–5 times/week	42 (678)	45 (3636)	0.87 (0.74,1.03), 0.1

^Days at hospital at least 3 days before debut year.
*Odds ratio **Confidence interval ***Oral hypoglycaemic agents.
CHD + T2DM: Congenital Heart Disease and Type 2 Diabetes Mellitus, Controls: Patients with T2DM only.

T2DM is frequently diagnosed in connection with hospitalization for other diseases, therefore the incidence of other cardiovascular diseases the year before T2DM was diagnosed was examined (Table 9). Hospitalization due to congestive heart failure (2.4 vs 0.91 %, P<0.001) and atrial fibrillation (3.2 vs. 0.77 %, P<0.001) were significantly more prominent during the year before onset of T2DM in CHD patients compared to patients with only T2DM. Also, the observation period was extended back to 1987, with similar findings as a result (Table 10). In addition, stroke was significantly more prevalent among CHD patients with T2DM as compared with patients with only T2DM from 1987 to the year of diabetes diagnosis (13.3 vs 4.0 % , P<0.001, Table 10).

TABLE 9. Incidence of cardiovascular diseases one year before year of T2DM onset.

Disease	CHD + T2DM % (n)	T2DM % (n)	P value
Ischaemic heart disease	1.9 (16)	1.8 (76)	0.9
Atrial fibrillation	3.2 (27)	0.77 (32)	<0.001
Heart Failure	2.4 (20)	0.91 (38)	<0.001
Stroke	0.60 (5)	0.77 (32)	0.6
PCI	0.36 (6)	0.67 (28)	0.3
CABG	0.48 (4)	0.34 (14)	0.5*
Renal failure	0.24 (2)	0.07 (3)	0.2*
Any CVD	2.9 (24)	2.9 (121)	1

*Fisher exact test.
CHD + T2DM: Congenital Heart Disease and Type 2 Diabetes Mellitus, Controls: Patients with T2DM only, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting, CVD: Cardiovascular disease.

TABLE 10. Cumulative incidence of cardiovascular diseases from 1987 to year of T2DM diagnosis

Disease	CHD + T2DM % (n)	T2DM % (n)	P value
Ischaemic heart disease	12.7 (106)	11.0 (460)	0.2
Atrial fibrillation	10.9 (91)	3.2 (131)	<0.001
Heart failure	10.6 (88)	3.8 (157)	<0.001
Stroke	13.3 (111)	4.0 (165)	<0.001
PCI	2.5 (22)	3.2 (131)	0.4
CABG	3.7 (31)	3.2 (132)	0.4
Renal failure	0.84 (7)	0.46 (19)	0.2
Any CVD	24 (200)	15 (623)	<0.001

CHD + T2DM: Congenital Heart Disease and Type 2 Diabetes Mellitus, Controls: Patients with T2DM only, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting. CVD: Cardiovascular disease.

When investigating the mortality from onset of T2DM to the end of follow-up on 30 June 2012 the mortality was higher in patients with CHD and T2DM (218/833 patients) compared to only T2DM (828/4,165 patients), 26.2% vs 19.9% , P<0.05). Even the log rank survival estimate differed significantly with higher mortality for CHD patients with T2DM compared to patients with only T2DM (P<0.001, Fig 9). This was evident already at five years after onset of diabetes; five-year mortality rates were 5.2 versus 3.4%, P<0.001, ten-year mortality was 13.7% versus 9.7% (P<0.001).

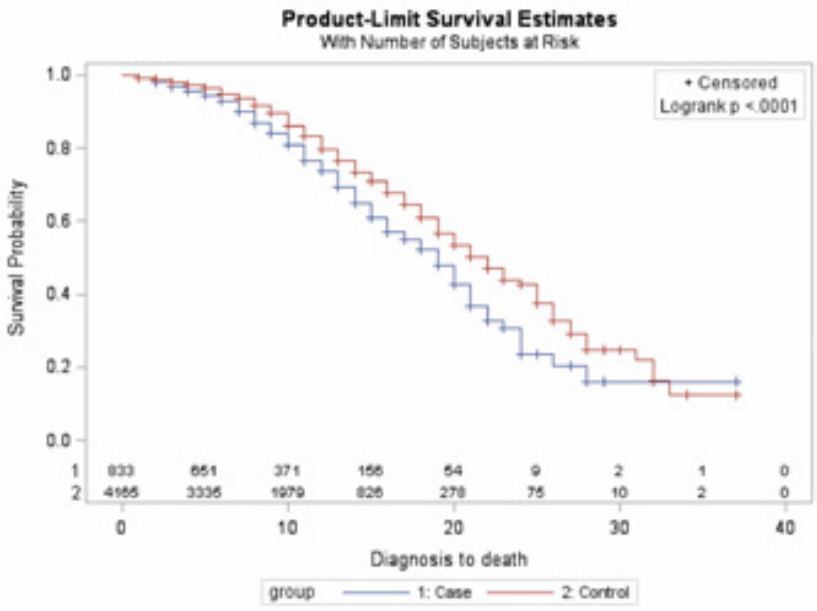


FIGURE 9. Kaplan–Meier survival estimate since onset of type 2 diabetes (years). Cases: adult patients with congenital heart disease and type 2 diabetes. Controls: patients with type 2 diabetes only.

5.2 PAPER II

5.2.1 BASELINE CHARACTERISTICS

In paper II, the two registers, NDR and NPR were linked, and 423,481 adult individuals with DM (type 1 or 2), in total were found. Of them, 1,860 adults with DM and CHD were identified. According to the T1DM definition of this paper, 255 individuals with CHD and T1DM with known year of onset of T1DM were found. As a control group 45,100 randomly selected patients without CHD and known year of onset of T1DM were found in the NDR. After patients were excluded according to the criteria described in the method section, a final study cohort of 104 individuals with T1DM and CHD (50 women and 54 men), was compared with 520 (250 women and 270 men) matched controls with T1DM, but without CHD (Fig 6.). Mean age at the last follow-up was 36.3 years among patients with T1DM and CHD compared with 35.3 years in controls (P=0.56, Table 11).

5.2.2 THE PREVALENCE OF T1DM

The estimated numbers of CHD patients in Sweden were at this time, 17,436 adult patients using the nationwide SWEDCON quality register. The number of Swedish CHD patients with T1DM, as determined by the present registers in the method section, was 255 individuals (Fig 6.). Based on these numbers, the estimated prevalence of T1DM is 1.5% among CHD patients (i.e. 255/17,436). To put this in relation to

international data, applying a population-based estimate from Canada with a CHD prevalence of 0.4% on the adult population in Sweden, this estimate would instead indicate that there are 32,000 adult patients with CHD in Sweden. The prevalence of T1DM could then be calculated to be 0.8% among Swedish patients with CHD compared with the estimated prevalence of 0.59 % (45,100/7,627,772) in patients with T1DM without CHD in Sweden 2012.

5.2.3 THE MORBIDITY BEFORE T1DM ONSET

T1DM is in some cases diagnosed in connection with hospitalization for other diagnoses and hospitalizations for other cardiovascular diseases the year before onset of T1DM was examined in the two groups. However, there were no apparent differences in diseases occurring before the onset of diabetes in this study.

TABLE 11. Characteristics and follow-up of the patients with T1DM and CHD.

Characteristics	Cases	Controls	P
Numbers of patients (women/men)	104 (50/54)	520 (250/270)	>0.99
Age at diabetes onset (years)	13.9	17.4	<0.001
Age at last follow-up (years)	36.3	35.3	0.56
Diabetes duration (years)	22.4	18.1	0.01
Follow up after onset of T1DM (years)	24.0	21.3	0.10

Cases: Patients with Type 1 Diabetes Mellitus (T1DM) and Congenital Heart Disease (CHD). Controls: Patients with T1DM without CHD.

5.2.4 THE MORBIDITY AND MORTALITY

In paper II, we described that patients with CHD had a lower age at onset of T1DM (13.9 vs. 17.4 years, P<0.001) compared to the controls with T1DM but without CHD. Consequently, patients with T1DM and CHD had a longer duration of T1DM follow-up compared to patients with T1DM but no CHD (22.4 vs. 18.1 years, P=0.01, Table 11).

Patients with CHD and T1DM had a higher rate of co-morbidities, expressed as a higher number of hospitalizations per patient (5.28 vs 3.12 P=0.001) with a discharge diagnosis of CHD, IHD, heart failure (9% vs. 2%, P=0.02), atrial fibrillation (7% vs 3%, P<0.001), stroke (6% vs. 2%, P=0.048), PCI, CABG, or renal failure, after onset of T1DM compared with controls. Patients with CHD and T1DM also had a higher rate of hospitalizations of at least 4 days per patient, in the year after diagnosis of T1DM (0.74 vs 0.63, P=0.03, Table 12). Heart failure was more frequently diagnosed in patients with CHD and T1DM (9 % vs 2 %, P=0.002) as well as stroke (6 % vs 2 %, P=0.048) and CVD (14 % vs 8%, P=0.04) compared to patients with T1DM without CHD. There was a trend for a higher rate of coronary artery disease after onset of T1DM. The mortality in patients with CHD and T1DM was 3 times higher compared to patients with T1DM without CHD (16% vs. 5%, p<0.001, Table 12).

TABLE 12. Characteristics of patients with T1DM and CHD after onset of T1DM.

Characteristics	Cases	Controls	P
Number of hospitalizations[1]	5.28	3.12	<0.001
Days of hospitalization[2]	0.74	0.63	0.03
Malignancy (%)	4	2	0.3
CAD (%)	12	6	0.06
Heart failure (%)	9	2	0.002
Stroke (%)	6	2	<0.05
Retinopathy (%)	9	8	0.7
Atrial fibrillation (%)	7	3	<0.001
Endocarditis (%)	1	0	0.2
CVD (%)	14	8	0.04
Mortality (%)	16	5	<0.001

Cases: Patients with Type 1 Diabetes Mellitus (T1DM) and Congenital Heart Disease (CHD), Controls: Patients with T1DM without CHD, CAD: Coronary Artery Disease, CVD: Cardiovascular disease.
[1] Number of times visiting the hospital for at least 4 days.
[2] Days at hospital for at least 4 days after the year of onset of T1DM.

In paper II, the characteristics of the cohort at the last follow up were investigated and patients with CHD and T1DM tended to have higher HbA1C levels, lower systolic blood pressure, and were less frequently smokers compared to patients with T1DM without CHD. Numerical differences regarding several clinical parameters were small and nonsignificant. However, retinopathy was significantly more common in patients with T1DM and CHD compared with those with T1DM without CHD (64% vs. 43%, P=0.02, Table 13). As a kidney function measurement, the creatine levels were observed to be lower in the patients with CHD and T1DM compared to the controls (88 µmol/L vs 93.4 µMol/L, P=0.03).

Paper II, described the extent of physical activity, which was similar with no clear differences between patients with T1DM with or without CHD (Table 14). Also, medication was similar between the groups, however a trend of higher rate of aspirin use was observed in patients with T1DM and CHD than in those with T1DM without CHD (Table 15).

5.3 PAPER III

5.3.1 BASELINE CHARACTERISTICS

In paper III, 21,982 patients with CHD were identified from the NPR, compared to 219,816 population based controls without CHD, 48.5% women. Divided by birth cohorts, mean age at the last follow-up in the first birth cohort (1970-1984) was 32.2 (SD 8.7) years in the patients with CHD and 34.4 (SD 4.5) years in the control cohort without CHD from the general population. In the second birth cohort (1985-1993) the mean age at follow up was 21.4 (SD 4.5) years for patients with CHD and 22.1 (SD 2.6) years for controls (Table 16).

TABLE 13. Characteristics of the patients with T1DM and CHD at last follow-up

Characteristics	Cases	Controls	P
Cumulative BMI	26.2	26.7	0.4
HbA1c (mmol/mol)	70.1	66.7	0.07
Systolic blood pressure (mmHg)	122.1	125.8	0.06
Diastolic blood pressure (mmHg)	71.3	72.5	0.2
Smoking (%)	10	18	0.07
Cumulative microalbuminuria (%)	20	19	>1
Waist measurement (cm)	88.0	93.4	0.08
Creatinine (µmol/L)	83.5	74.1	0.03
Micro- or macroalbuminuria (%)	29	26	0.2
Microalbuminuria (%)	13	13	>1
Macroalbuminuria (%)	9	7	0.5
Retinopathy (%)	64	43	0.02

Cases: Patients with Type 1 Diabtes Mellitus (T1DM) and Congenital Heart Disease (CHD).
Controls: Patients with T1DM without CHD.

TABLE 14. Physical activity in patients with T1DM and CHD

Category (times/week)	Cases	Controls	P
1 (never)	0.12	0.12	
2 (1)	0.19	0.16	
3 (1–2)	0.24	0.27	
4 (3–5)	0.24	0.24	
5 (daily)	0.22	0.21	
Chi-square test			0.9544

Cases: Patients with Type 1 Diabtes Mellitus (T1DM) and Congenital Heart Disease (CHD).
Controls: Patients with T1DM without CHD.

TABLE 15. Medications of patients with T1DM and CHD.

Medication	Cases	Controls	P
Hypertensive medication (%)	30	26	0.5
Lipid-lowering medication (%)	25	19	0.2
Aspirin (%)	19	12	0.07

Cases: Patients with Type 1 Diabtes Mellitus (T1DM) and Congenital Heart Disease (CHD).
Controls: Patients with T1DM without CHD.

TABLE 16. Baseline characteristics of the study population by CHD and controls divided by birth cohort and lesion group

Characteristics	Case	Control	P
	(N=21982)	(N=219816)	
GENDER			>0.999
Men	11331 (51.5%)	113319 (51.6%)	
Women	10650 (48.5%)	106497 (48.4%)	
Age at end of study	27.0 ± 8.9	28.5 ± 7.2	<0.001
Born in Sweden			0.028
No	1843 (8.4%)	17499 (8.0%)	
Yes	20139 (91.6%)	202317 (92.0%)	
BIRTH COHORT			>0.999
1970-1984	11508 (52.4%)	115079 (52.4%)	
Age at end of study	32.2 ± 8.7	34.4 ± 4.5	<0.001
1985-1993	10474 (47.6%)	104737 (47.6%)	
Age at end of study	21.4 ± 4.5	22.1 ± 2.6	<0.001
CHD CLASSIFICATION			>0.999
ASD	2405 (10.9%)	24049 (10.9%)	
CoA	1306 (5.9%)	13060 (5.9%)	
Conotruncal defects	2022 (9.2%)	20230 (9.2%)	
Other	10793 (49.1%)	107918 (49.1%)	
Severe non-conotruncal defects	1087 (4.9%)	10870 (4.9%)	
VSD	4369 (19.9%)	43689 (19.9%)	
LESION BY SEVERITY			0.993
Complex	4415 (20.1%)	44160 (20.1%)	
Non-Complex	17567 (79.9%)	175656 (79.9%)	

CHD = Congenital heart defect ASD = Atrial septal defect, CoA = Coarctation of the aorta, VSD = Ventricular septal defect

5.3.2 THE PREVALENCE AND INCIDENCE OF T1DM

Of patients with CHD in the cohort, 221 (1%) adults were diagnosed with T1DM, compared to 1553 (0.7%) of the general population-based controls (OR 1.46, P<0.001). The incidence rate of T1DM was higher among all patients with CHD (born 1970-1993), 3.7 vs 2.5/10,000 person years among controls, with a HR of 1.50 (95% CI 1.3 – 1.73) (Fig. 7, Tables 17 and 18).

The incidence rate of T1DM overall, was higher in both of the birth cohorts throughout the study in patients with CHD compared to population based controls (Fig. 7, Table 17).

TABLE 17. Incidence rate of T1DM and mortality by birth cohort

		All			1970-1984			1985-1993		
	Group	N	Pyrs	IR 95% CI	N	Pyrs	IR 95% CI	N	Pyrs	IR 95% CI
CHD to T1DM	Case	221	590716	3.7 (3.3-4.3)	137	367861.0	3.7 (3.1-4.4)	84	222855	3.8 (3.0-4.7)
	Control	1553	6251627	2.5 (2.4-2.6)	785	3940993.7	2.0 (1.9-2.1)	768	2310633	3.3 (3.1-3.6)
CHD to death	Case	1654	590716	28.0 (26.7-29.4)	1157	367861.0	31.5 (29.7-33.3)	497	222855	22.3 (20.4-24.4)
	Control	1080	6251627	1.7 (1.6-1.8)	766	3940993.7	1.9(1.8-2.1)	314	2310633	1.4(1.2-1.5)
T1DM to death	Case	20	3025	66.1 (40.4-102.1)	17	2123.7	80.0 (46.6-128.2)	3	902	33.3 (6.9-97.2)
	Control	32	21514	14.9 (10.2-21.0)	27	13533.0	20.0 (13.1-29.0)	5	7981	6.3 (2.0-14.6)

CHD=Congenital Heart Disease, Pyrs=person-years, T1DM=Type 1 Diabetes Mellitus, IR=Incidence rate/ 104 pyrs, CI = Confidence Interval

The described risk of T1DM in paper III, was increased among patients with CHD compared to the matched controls in the first birth cohort, with an incidence rate of 3.7 vs 2.0 T1DM onsets per 10,000 person-years, and a risk almost twice among CHD patients than that of the matched controls (HR 1.9, 95% CI 1.55-2.24, Table 17, 18, Fig. 10).

TABLE 18. Risk of T1DM and mortality among patients with CHD by birth cohort

	All		1970-1984		1985-1993	
	*HR (95 % CI)	P-value	*HR (95 % CI)	P-value	*HR (95 % CI)	P-value
CHD to T1DM	1.50 (1.31–1.73)	<0.001	1.87 (1.56–2.24)	<0.001	1.14 (0.91–1.42)	0.3
CHD to Death	16.19 (15.00–17.48)	<0.001	16.14 (14.73–17.69)	<0.001	16.34 (14.19–18.82)	<0.001
T1DM to Death	4.21 (2.40–7.37)	<0.001	4.06 (2.21–7.47)	<0.001	5.18 (1.24–21.72)	0.03

*Adjusted for gender
CHD = congenital heart disease, T1DM = Type 1 Diabetes Mellitus, HR = Hazarad Ratio, CI = Confidence Interval, reference = control, reference = control with no CHD

However, the difference in incidence rate of T1DM was numerically smaller and not statistically significant in the second birth cohort (HR 1.14, 95% CI 0.9-1.41, Table 17, Fig. 10). The cumulative probability of T1DM onset by birth cohort, compared to matched controls, during the up to 42 years follow up period is shown in (Fig. 10).

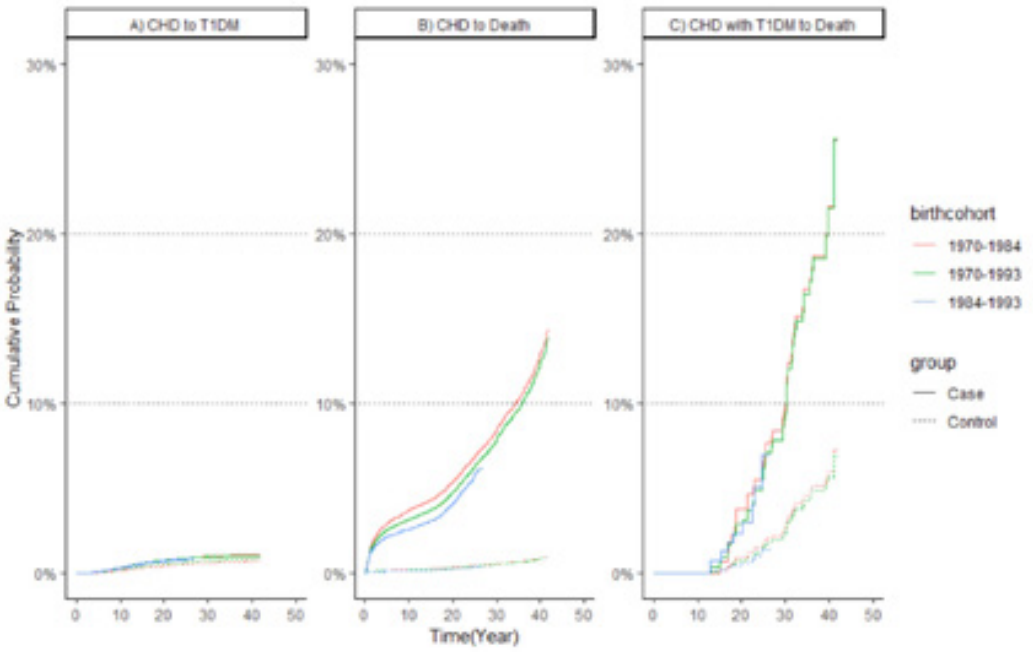


FIGURE 10. The cumulative probability of Type 1 Diabetes Mellitus (T1DM) and death by birth cohort. In a multistate cox regression model, patients with congenital heart disease(CHD) had a higher cumulative probability of developing T1DM in both birth cohort groups compared to the controls. Patients with CHD had a significant higher mortality compared to the controls. Patients with CHD and T1DM had even more increased mortality compared to patients with T1DM and controls.

As a post-hoc analysis, with the follow-up time divided into intervals (0-4, 5-9, 10-17 and 18+ years) in the multistate model, the incidence of T1DM was significantly higher after 10-17 years of follow-up for patients with CHD (HR 1.44 after 10-17 years, HR 1.88 after 18+ years, P<0.001) compared to controls. This pattern was seen in both birth cohorts but was significant only in the first birth cohort (HR 1.93 after 10-17 years, HR 2.12 18+ years, P<0.001, Table 19).

TABLE 19. Risk of T1DM and mortality among patients with CHD by birth cohort and time intervals

Group	HR	95% LCL	95% UCL	P-value
ALL				
CHD to Diabetes				
0-4 yrs	1.12	0.68	1.85	0.7
5-10 yrs	1.34	0.98	1.83	0.07
10-17 yrs	1.44	1.15	1.81	<0.001
18+ yrs	1.88	1.47	2.40	<0.001
CHD to Death				
0-4 yrs	112	88	141	0
5-10 yrs	34.7	25.2	47.8	<0.001

TABLE 19 (CONTINUED). Risk of T1DM and mortality among patients with CHD by birth cohort and time intervals

Group	HR	95% LCL	95% UCL	P-value
10-17 yrs	12.6	10.3	15.4	<0.001
18+ yrs	6.28	5.59	7.05	<0.001
Diabetes to Death				
0-4 yrs	-	-	-	-
5-10 yrs	-	-	-	-
10-17 yrs	10.9	2.4	48.8	<0.001
18+ yrs	3.60	1.95	6.65	<0.001
1970-1984				
CHD to Diabetes				
0-4 yrs	0.70	0.25	1.93	0.5
5-10 yrs	1.70	1.09	2.67	0.02
10-17 yrs	1.93	1.41	2.63	<0.001
18+ yrs	2.12	1.62	2.77	<0.001
CHD to Death				
0-4 yrs	213	142	318	<0.001
5-10 yrs	48.4	31.4	74.6	<0.001
10-17 yrs	15.5	11.8	20.3	<0.001
18+ yrs	6.88	6.07	7.81	<0.001
Diabetes to Death				
0-4 yrs	-	-	-	-
5-10 yrs	-	-	-	-
10-17 yrs	6.63	0.93	47.1	0.06
18+ yrs	3.86	2.03	7.34	<0.001
1985-1993				
CHD to Diabetes				
0-4 yrs	1.38	0.77	2.45	0.3
5-10 yrs	1.10	0.71	1.70	0.7
10-17 yrs	1.09	0.78	1.53	0.6
18+ yrs	1.13	0.61	2.10	0.7
CHD to Death				
0-4 yrs	62.4	46.4	83.8	<0.001
5-10 yrs	20.7	12.7	33.7	<0.001
10-17 yrs	9.67	7.13	13.1	<0.001
18+ yrs	3.86	2.84	5.25	<0.001
Diabetes to Death				
0-4 yrs	-	-	-	-
5-10 yrs	-	-	-	-
10-17 yrs	19.2	1.74	212	0.02
18+ yrs	2.02	0.23	18.1	0.5

5.3.3 MORTALITY

In paper III, the mortality risk was described and calculated to be 16 times higher in patients with CHD compared to the controls (HR 16.19, 95% CI 15.00-17.48, Table 18, Fig. 10). Of patients with CHD and T1DM, 20 (9%) patients died during the follow-up period compared to 32 (2%) of the controls with T1DM (OR 4,39 P<0.001). Of patients without DM, 1,654 (7,6%) patients with CHD died compared to 1,080 (4,9%) controls during the follow-up time (OR 16.5, P<0.001). The total mortality among patients with CHD was four times higher, compared to controls (HR 4.21, 95% CI 2.40-7.37, Table 17, 18, Fig. 10) after onset of T1DM, and with a mortality rate of 2,414 vs 543/10,000 person years, respectively.

When divided by birth cohort, the mortality rate in patients with CHD and T1DM was four times higher in the first birth cohort compared to the controls with T1DM (HR 4.06, 95%CI 2.21-7.47, Table 17, 18) with a mortality rate of 80 vs 20 /10,000 person-years. At the same time, the calculated mortality rate in the second birth cohort was 5 times higher, 33.3 vs 6.3/10,000 person-years (HR 5.18, 95%CI 1.24-21.72, Table 17, 18) compared to the controls. The cumulative probability of mortality by birth cohort during the 42-year follow up period is shown in Fig. 10.

As a post-hoc analysis, with the follow-up time divided into intervals (0-4, 5-9, 10-17 and 18+ years after birth) in the multistate model, the mortality for all patients with CHD was significantly increased compared to the general population based controls without CHD for all year intervals. However, the highest mortality was seen in the first years of age and then slowly decreased (HR 112 after 0-4 years, HR 34,7 after 5-10 years, P<0.001). The significantly increased mortality for CHD patients compared to the controls was seen in both birth cohorts but higher in the first birth cohort (HR 213 after 0-4 years, HR 48.4 after 5-10 years, P<0.001) than in the second birth cohort (HR 62.4 after 0-4 years, HR 20.7 after 5-10 years, P<0.001) compared to controls (Table 19). After developing T1DM, patients with CHD and T1DM had the highest mortality rate after 10-17 years after T1DM onset with a more than 10 fold mortality rate (HR 10.9, CI 2.4-48.8, P<0.001). This high mortality rate was also seen in patients with CHD and T1DM divided by birth cohort but was only significant in the first birth cohort (HR 3.86, CI 2.03-7.34, P<0.001, Table 19).

5.4 PAPER IV

5.4.1 BASELINE CHARACTERISTICS

From the National Patient Register, patients with CHD, born 1930-1983 and that had reached at least 35 years of age were identified. Mean birth year was 1959 (SD 15). Divided by lesion group the most common were atrial septal defect (lesion group 5) and other heart and circulatory system anomalies (lesion group 6) (Table 1, Paper IV, Table 5).

5.4.2 THE PREVALENCE AND INCIDENCE OF DM

Of adult patients with CHD, 8.4% were diagnosed with DM, compared to 5.7% of the controls (OR 1.6, P<0.001, Table 1, paper IV, Fig 1, paper IV).

The incidence rate of DM was overall higher among patients with CHD (Tables 2 and 3, paper IV). In overall, the risk of DM was higher throughout the study in patients with CHD compared to controls (Table 2 and 3, paper IV). This higher DM incidence ratio remained significant also when adjusted for hypertension and or hyperlipidemia (Table 2 and 3, paper IV, Appendix C, paper IV).

Divided by birth cohorts, the risk of DM was higher among patients with CHD compared to the matched controls in both birth cohorts but most increased in the second birth cohort (Table 2 and 3, paper IV). The cumulative probability of DM by birth cohort during the up to 87 years follow up period is shown in Fig. 3, paper IV.

There was no difference in incidence rate of DM between men and women, although the risk of developing DM was higher in both women and men with CHD compared to controls (Table 2 and 3, paper IV).

Divided by lesion group of CHD, the incidence rate of DM was higher in all patients with a CHD diagnosis compared to the population-based controls. However, incidence ratio of DM increased with complexity of CHD with the highest risk of DM in patients with conotruncal defects (Table 2 and 3, paper IV). The smallest difference in incidence rate of DM was found in atrial septal defects (Table 2 and 3, paper IV)

5.4.3 MORTALITY

Of patients with CHD, 36 % adults who were diagnosed with DM died during the follow-up time, compared to 31 % of the controls (Table 1, Fig 1, paper IV).

After onset of DM, the total mortality among patients with CHD was significantly higher compared to controls (Table 4-5, Fig. 4, paper IV) and remained significant also when adjusted for hypertension and hyperlipidemia, Appendix E.

The risk of mortality in patients with CHD and DM was significantly increased in both birth cohorts and the risk of mortality was almost doubled in men in the second birth cohort, 1960-1983 (Table 4-5, paper IV) compared to controls.

The cumulative probability of mortality by birth cohort during the 87-year follow up period is shown in Fig. 4, paper IV.

The risk of mortality in patients with CHD and DM compared to population-based controls and divided by lesion group of CHD is seen in Table 5, paper IV. Although it was not statistically significant for all different lesion groups separately, the highest risk of mortality was seen in patients with conontruncal defects, lesion group 1, and the smallest increase in risk was seen in atrial septal defects, lesion group 5. The only significant difference in mortality was seen in lesion group 6, other heart and circulatory system anomalies, and was seen for both nonadjusted and values adjusted for hyperlipidemia and hypertension before onset of DM compared to controls (Table 4-5, Appendix D, paper IV)

Incidence ratio of a composite of heart failure, stroke, myocardial infarction and death is presented in fig 5 and appendix E, paper IV.

For detailed results of paper IV, see Papers, paper IV.

6 DISCUSSION

6.1 CHD, T1DM AND T2DM AND THE METHODOLOGY CHALLENGES OF THIS THESIS

Due to advances in diagnostics, surgical techniques and medical care in the last decade, life expectancy has significantly increased for patients with CHD with 95-97% of all live born infants surviving into adulthood and this number is likely to increase further with even more advanced and specialized care. These numbers, has resulted in a large adult CHD population [25, 28]. Still, patients with a non-complex and more benign lesion like atrial or ventricular septal defects live longer and have a longer life expectancy compared to a more complex CHD like tetralogy of Fallot or coarctio aorta. However, patients with both non-complex and complex CHD have a higher risk of comorbidity and death compared with the general population without CHD[12].

CHD has a relatively low prevalence in the population and large cohorts including large numbers of patients are needed to draw significant conclusions.

Although T2DM is increasing in the population, the prevalence is still relatively low, at the same time the prevalence of TIDM seems stable but even lower [59, 66, 107]. To study the impact of two diagnoses such as CHD and DM with a relatively low prevalence in a population, comparatively large studies are needed and a large number of patients are also needed to assess clinical characteristics, and to estimate the outcome in patients with the combined cardiovascular stress of CHD and DM. The presence and development of T1DM and T2DM in CHD patients have not been extensively studied but with the method of large national epidemiological cohort studies using large, trustful, national registers as NPR, NDR and CDR we were able to accomplish this, as presented in this thesis.

The study method that was used was analytical, retrospective cohort studies. A case-control study could be an option for a study of exposure in patients with and without the outcome of interest, however as described in the methods section, this was not chosen while we started with the exposure of CHD and treated DM as a second exposure and as an outcome and also measured mortality and comorbidities as outcomes. The cohort study design is also generally considered to have a higher scientific rigor and result in a higher level of evidence than case-control studies. Therefore, a cohort study design was

chosen, which also is the best method for this thesis to investigate upon a causality hypothesis of CHD, DM, mortality and morbidity. Although a causality between CHD and DM could never have been truly met due to the limitation of that patients are not randomized to get the CHD. A prospective cohort study design is the most reliable study design due to limitations and the ability of adjusting for confounders, bias and study errors. However, a retrospective cohort design was the only available study design due to limited time and budget for the research in this thesis.

With an elderly CHD population, the prevalence of age related diseases and T2DM has increased [108] and the increase in prevalence of T2DM observed in the general population today is most likely also to be seen among CHD patients. In a large national register, NDR, we were able to identify a large number of adult patients with T2DM and CHD. The exact prevalence of CHD in adults in Sweden is not known. Although, based on the national register results of this thesis [103] and in international, population-based databases [25], the prevalence of T2DM in CHD patients in Sweden can be estimated to be between 4.2 and 7.6%. Compared to pharmaco-epidemiological studies in Sweden, presenting the prevalence of T2DM to be 4.7% [70] our findings indicate at least a similar or higher prevalence of T2DM among CHD patients. This is important for caregivers to have in mind while treating and following CHD patients as they are likely to develop metabolic and cardiovascular diseases as the general population.

Meanwhile, T1DM is considered to be caused by an autoimmune reaction and exposure to infections and lifestyle changes, and increased physical and mental stress could contribute to an increased risk of developing T1DM. CHD in combination with T1DM in patients have to our knowledge not been extensively studied before. In papers II and III, it is discussed if there could be a connection between CHD and T1DM and if so, what the consequences could be. T1DM is a life threatening disease if it is not treated and therefor it is of importance to describe its prevalence to be aware of it and detect it as soon as possible, not least in a patient group that is already vulnerable and at risk for other cardiovascular complications [25].

The conventional risk factors are associated with the occurrence of additional coronary artery disease in CHD patients just as in the general population [109] and it has been suggested that coronary angiography should be routinely performed in CHD patients that have previously undergone cardiac surgery once they are above 40 years of age [110]. DM and its associated cardiac and vascular complications could speculatively be expected to have an even larger impact in the already vulnerable CHD population, especially given the expected need for repeat surgical or endovascular corrective interventions and it is of importance for clinicians to be aware of this and to detect DM in the CHD population in an early phase.

6.2 PAPER I

6.2.1 THE BASELINE CHARACTERISTICS

In paper I, the mean age of the patients with CHD and T2DM in the cohort was 70 years. This age reflects a large proportion of patients with more non-complex and benign lesions of CHD, such as atrial and ventricular septal defects. Almost a quarter of the patients in the cohort with CHD and T2DM consisted of patients with coarctation of the aortae, a macrovascular malformation that has been reported to be associated with atherosclerotic disease [111].

6.2.2 THE MORTALITY AND MORBIDITY

The prevalence of lifestyle risk factors in paper I suggests that a sedentary lifestyle may be an especially prominent problem in CHD patients. This is in line with findings from other studies [112] and a large observational study from the NDR of patients with T2DM showed considerably increased risks for cardiovascular disease and mortality with low physical activity [113]. It is known that obesity has a negative impact on early postoperative recovery among the general population and CHD patients are already believed to be at increased risk for cardiac surgery compared to the general population, although no direct influence on postoperative mortality has been shown [114]. Conventional risk factors will also apply to and affect CHD patients. However, the proportion has so far been relatively low, presumably due to the low mean age of CHD patients[115]. Paper I presented a comparatively high mortality with a five-year mortality rate of 5.2 versus 3.4% ($P<0.05$) for patients with CHD and T2DM compared to patients with only T2DM. Paper I lack a control group with CHD but without T2DM. Therefore, any conclusions regarding the impact of T2DM on mortality in patients with CHD could not be drawn since it is not possible to conclude whether the mortality is related mainly to the CHD itself or to the contribution of T2DM in patients with CHD. However, it would be surprising and counterintuitive, if adult patients with CHD were not adversely affected by the development of T2DM with an increased mortality and morbidity as a result. DM, both T1DM and T2DM, is associated with an increased risk of developing atherosclerotic disease, which was seen regardless of the presence of CHD since atherosclerotic manifestations were equally common among patients with CHD and T2DM compared to patients with only T2DM. At the same time, arrhythmias and heart failure were more common among patients with the combination of CHD and T2DM compared to patients with only T2DM. A conclusion of this would therefore be that the CHD cardiologist needs to be aware of the existence, and importance, of T2DM among elderly CHD patients.

In paper I, patients with CHD and T2DM were shown to be as likely to receive antihypertensive and lipid-lowering drugs compared to those with T2DM only. Somewhat unexpectedly patients with CHD and T2DM, were less frequently given aspirin compared to patients with T2DM only. An explanation for this may be more frequent use of warfarin for specific indications, namely, atrial arrhythmias and mechanical heart valves for patients with CHD. Today, Swedish national guidelines do not recommend aspirin for all patients with T2DM, the addition of other cardiovascular risk factors may warrant the prescription of aspirin for this at-risk group of patients [116, 117]. Paper I show less aspirin treatment for patients with combined CHD and T2DM, in combination with their substantially higher mortality than the control group with T2DM only, suggesting treatment with aspirin and lipid-lowering treatment as preventive care in patients with T2DM and CHD should be considered more prevalent.

6.3 PAPER II

6.3.1 THE BASELINE CHARACTERISTICS

In paper II, patients with CHD were seen to have an earlier onset of T1DM compared with patients with only T1DM in the NDR (13.9 vs. 17.4 years, P<0.001). The earlier onset of T1DM in patients with CHD could be due to increased physical and mental stress in these patients, as well as more illnesses and hospitalizations, possibly triggering the autoimmune reaction being the basis of T1DM. However, paper II did not show that patients with CHD had more severe illnesses and hospitalizations compared with controls during the year before onset of T1DM. While, our data only reflect severe conditions of illnesses that required hospitalization and were found in NPR it is still possible that patients with CHD may have had a higher rate of infections that did not require hospitalizations.

6.3.2 MORTALITY AND MORBIDITY

Mortality was significantly higher, 16 vs 5 %, in patients with the combination of T1DM and CHD compared with patients with only T1DM but the reason for the approximately three times higher mortality rate in patients with CHD and T1DM is unclear. However, this finding could potentially be explained by the additional effects of the CHD resulting in more vascular defects and harder to control T1DM and its complications. This is in line with paper 1 showing a high mortality for patients with T2DM and CHD as compared to patients with only T2DM [8]. The study in paper II did not include a control group with CHD, but without T1DM. Therefor we cannot draw any conclusions regarding the effect of the combination of T1DM and CHD on mortality and morbidity and the increased mortality in patients with T1DM and CHD could be related mainly to the CHD itself, rather than the combination of T1DM and CHD. Also, patients with T1DM have a higher mortality because of a higher risk of CVD [118]. Additionally, patients with CHD are likely to have at least the same effect of their T1DM and patients with the combination of T1DM and CHD had a significantly higher risk of subsequent morbidity (i.e., heart failure, CVD, and stroke).

The rate of CVD in patients with T1DM is higher in patients with a dysfunctional glycemic control [53]. In paper II, the metabolic situation for patients with combined T1DM and CHD and patients with only T1DM was similar, although there was a trend of higher HbA1C levels in patients with combined T1DM and CHD. Although similar metabolic control, the combination of T1DM and CHD generated a risk of CVD almost twice, 14 vs 8 % (P=0.04), the controls without CHD This could probably be due to CHD itself. However, the possibility that combined effects of CHD and T1DM will increase the risk of CVD could not be excluded.

A sedentary lifestyle in the general population as well as in patients with CHD is a prominent problem and a risk factor of CVD and mortality [112, 113]. In paper II both patients with combined T1DM and CHD as well as patients with only T1DM exercised to the same extent and patients with combined T1DM and CHD did not appear to exercise to a lower degree because of their CHD, suggesting that the level of physical activity is not affected by the presence of CHD. This is in line with no significant difference in cumulative body mass index or cumulative microalbuminuria.

Creatinine levels affect the risk for morbidity and mortality in adults with CHD [119] and patients with combined T1DM and CHD had significantly higher creatinine levels than those with only T1DM. This could reflect an earlier

onset of T1DM, and consequently longer duration of T1DM, which could also be reflected in the occurrence of a higher rate of retinopathy. However, the higher creatinine could also be due to CHD patients being exposed to more surgery and contrast in imaging procedures or due to the CHD itself [120].

6.4 PAPER III

6.4.1 THE INCIDENCE OF T1DM

The incidence of T1DM in CHD patients compared to population-based controls has not been extensively studied before. In paper III, patients with CHD had an almost 50 % higher incidence of T1DM compared to population-based controls, which is line with our previous data and paper II [121].This is the first time an increased incidence of T1DM has been reported for patients with CHD. The increased risk of developing T1DM in patients with CHD as seen in the cohort, could be due to increased physical and mental stress in patients with CHD, as well as more illnesses and hospitalizations. However, it could also be caused by genetics predisposing for both CHD and T1DM. The causality of genetics predisposing for both CHD and T1DM is purely speculative, but may suggest the existence of a genetic link between these two conditions and it could be important to investigate this further by CHD severity classification. There is also a lack of more detailed information on the impact of prognostic factors associated with CHD, such as exercise capacity, number and complexity of previous surgeries, which could contribute to our understanding regarding if a severe and complex CHD, resulting in hypoxia, could contribute to a pancreas insufficiency and DM in patients with CHD. This would be valuable to investigate further. However, this level of detailed analysis was not possible in paper III, while the number with specific CHD diagnoses and T1DM was limited as well as some of these variables not being available.

Divided by birth cohort, the increased risk of developing T1DM was primarily seen among patients with CHD from the first birth cohort, born between 1970-1984. However, in the second birth cohort the risk of developing T1DM was numerically smaller and not statistically significant compared to population based controls. The explanation for this finding is not clear, but one may speculate that patients in the first birth cohort were more likely to spend more time in hospital, having more infections and stress than the second birth cohort, possibly triggering an autoimmune T1DM onset. However, the increased incidence of T1DM could also be due to that the second birth cohort had shorter follow up time, resulting in fewer T1DM diagnosis making any differences between the groups become smaller because of the fewer events. The registration of T1DM may potentially have been less accurate for population-based controls than for CHD patients, already followed in in- and -outpatient care, in the first birth cohort and the relative increase among controls in incidence of T1DM in the second birth cohort may at least partially be an effect of better registration.

For the whole cohort and divided by birth cohort, a post-hoc analysis divided the follow-up time into year intervals to be analyzed in the multistate model presenting a significantly higher incidence of T1DM in patients with CHD after 10 years of age compared to the controls. This could be due to the time it takes to develop T1DM due to infections and stress strain among patients with CHD. It could be that the results were not significantly different in earlier years because of the lack of cases, suggesting T1DM to not be triggered by CHD in the early patient years.

6.4.2 MORTALITY

In paper III, the mortality was 16 times increased in patients with CHD compared to the controls, which is line with earlier studies [12]. The highest mortality was seen the first years of having CHD and then slowly decreased. The significant increase in mortality for CHD patients compared to the controls was seen in both birth cohorts but higher in the first birth cohort than in the second birth cohort, suggesting decreased mortality with improved medical and surgical care in recent years in patients with CHD. However, an association of DM, CHD and mortality has been observed by some authors. In a large registry study from Germany, Engeling et al. suggested DM to be a non-significant risk factor for death among 2,596 adult patients with CHD, mean age 33-39[40]. In paper III, patients with T1DM and CHD had an increased mortality after 10 years of age compared to those with T1DM without CHD. The more than four times increased mortality risk for patients with T1DM and CHD may be caused by the combined effects of cardiovascular and metabolic disease. Each making the other more difficult to deal with and increasing the risk for early and late complications, which is in line with previous studies [8, 121].

Although, the increased mortality in patients with T1DM and CHD seems mostly related to the presence of CHD itself, our data indicate that the combination of T1DM and CHD is associated with higher mortality than either disease alone. This is in line with earlier studies presenting that patients with T1DM have higher mortality due to a higher risk of cardiovascular disease [122]. Indicating a higher CVD and mortality risk in patients with CHD and T1DM than either diagnosis on its own.

6.5 PAPER IV

6.5.1 BASELINE CHARACTERISTICS

The large retrospective cohort design study in paper IV, describing the prevalence, incidence and mortality in patients with CHD and DM over up to 87 years follow up time, 1930-2017 found that the prevalence at the end of the study period of DM with onset after 35 years of age was 1.6 times higher in patients with CHD compared to the general population-based controls. The higher prevalence is in line with one of our earlier studies and paper I, where we estimated the prevalence of T2DM to be between 4.2-7.6% of adult CHD patients in Sweden [8]. However, the prevalence of DM in the general population without CHD was also slightly higher than what has been reported in the Swedish National Diabetes Register NDR. However, in the current study we were not able to distinguish all patients with T2DM from those with T1DM because separate ICD-codes were not available in ICD-8 and ICD-9. Although, more than 93% of the patients with DM in the current dataset are believed to have T2DM according to earlier findings [66].

Most of the patients in our study had non-complex or mild CHD, representative for the CHD population in general. Still patients with CHD had more prior CVD, hyperlipidemia and coronary intervention compared to population-based controls without CHD.

6.5.2 THE INCIDENCE OF DM

In paper IV, patients with CHD had a significantly higher risk of developing DM compared to the general population without CHD. Divided by CHD lesion, patients with a more complex CHD were more likely to develop DM. This is in line with a previous population based study, Madsen et.al, presenting CHD patients >30 years

of age in Denmark to have an higher risk of developing T2DM compared to the general population (HR 1.4, 95% CI 1.1–1.6) and in particular CHD patients who had cyanotic defects were more likely to develop T2DM compared subjects with acyanotic CHD (hazard ratio 1.9, 95% CI 1.1–3.3) [123].

The higher risk of DM, primarily T2DM, in patients with CHD could be due to lifestyle factors [8, 90, 124, 125], metabolic syndrome or it could be due to a genetic predisposition for both CHD and DM. A more complex CHD may be associated with a sedentary lifestyle but several studies have reported a lower BMI and less overweight among adults with CHD [124, 126]. The risk of DM in patients with CHD in our study remained significantly higher also if adjusted for hypertension and/or hyperlipidemia indicating that CHD alone could contribute to development of DM without the metabolic syndrome. Also, the risk of DM increased with severity of CHD which could be due to a more sedentary lifestyle in this patient group or tentatively suggest the possibility of a genetic relationship between CHD and DM to be important.

Divided by birth cohorts, the highest risk of DM was seen in the second birth cohort and this pattern was also seen among the matched controls for the second birth cohort which is in line with the globally increasing incidence of T2DM in the younger population [47].

6.5.3 MORTALITY

We have in prior studies described the mortality to be 16 times increased in patients with CHD and T1DM compared with controls [127], which also is in line with other studies [12]. However, the association of overall DM, CHD and mortality was also studied in a large registry study from Germany which found that DM was a non-significant risk factor for death among 2,596 adult patients with CHD, mean age 33-39, although no significant correlation could be established[40]. In paper IV, the mortality was higher in patients with DM and CHD compared to population-based controls with DM without CHD. The same pattern was seen also when adjusted for hypertension and hyperlipidemia, suggesting the increased risk to be due to the combination of CHD and DM rather than merely to the metabolic disease on its own. The composite endpoint is discussed more in paper IV.

The higher mortality risk for patients with DM and CHD may be caused by the combined effects of cardiovascular and metabolic disease, increasing the risk for early and late complications, which is in line with previous studies[8, 121, 125]. The higher mortality in patients with DM and CHD seems mostly related to the presence of CHD itself, although our data indicate that the combination of DM and CHD is associated with higher mortality than either disease alone. This is in line with earlier studies presenting that patients with T2DM have higher mortality due to a higher risk of cardiovascular disease[128].

For detailed discussion of paper IV, see Papers, paper IV.

7 LIMITATIONS

7.1 EPIDEMIOLOGY STRENGTHS AND LIMITATIONS

The thesis is based on retrospective cohort design studies and epidemiologic data. The strength in epidemiological studies is the ability to study the whole population without categorizing, giving a better understanding about the population overall. This category of research always has the overall limitation that one cannot show a causal relation in the same manner as in prospective randomized controlled studies, and there is always a higher risk of false positive findings, as in randomized studies, without true underlying causality, than in randomized studies. However, in clinical randomized studies a cohort of the population is selected, giving some selection bias of why the participations participate in the study.

7.1.1 ERROR TYPES AND MASS SIGNIFICANCE

As always, when working with hypotheses and significance testing (p-value) there is always a risk of type 1 and type 2 errors (Table 20). In terms of false positives and false negatives, a positive result is seen to reject the H0, while a negative result is seen to fail to reject the H0. When rejecting H0 there is always a risk of rejecting a true H0 as a test procedure, meaning a false positive or type 1 error. In terms of this thesis it would be the H0 that CHD patients do not have an increased risk of DM, mortality or morbidity compared to patients without CHD. On the other

hand, a false negative or type 2 error is a failure to reject a true false H0 in a study, which in this thesis would be to not be able to disprove that patients with CHD do not have increased risk of DM even if this is truly false. As the thesis rely on cohort register studies, it was not possible to get access to the individual patient medical charts and control the outcome. Although, to reduce the risk of committing a Type I error, the type I error rate or significance level (P) is the probability of rejecting the H0 given that it is true. In this this thesis, the p-value and the significance level are set to 0.05 (5%), implying that it is acceptable to have a 5% probability of incorrectly rejecting the true H0. Type II error is closely associated with analyses' power and to reduce this it is possible to increase the test's sample size or relaxing the p-value and thereby increase the analyses' power. A test statistic is seen as robust if the Type I error rate is controlled. In this thesis we have also been using CI to see how the true result may vary from the estimate to be able to describe the outcome reliability[6].

TABLE 20. Type 1 and Type 2 Errors

Decision about null hypothesis (H0)	H0	H0
	True	False
		Type II error
Don't reject	Correct inference	(false negative)
	(true negative)	(probability = β)
	(probability = 1 - α)	
	Type I error	Correct inference
Reject	(false positive)	(true positive)
	(probability = α)	(probability = 1 - β)

As always when analyzing multiple variables and testing multiple hypotheses in large cohorts there is always a probability of mass-significance, meaning that in the significance testing of many hypotheses at a given significance level there is a higher risk of incorrectly rejecting one or more true H0. This is a complex problem and the risk exists independent of the significance level. To get around this problem it is possible to adjust for this (e.g. by Bonferroni adjustment) or as in this thesis distinguish between hypothesis testing (what has been done) and hypothesis generating studies. Where hypothesis testing is when you test the hypothesis, the study design to test, and hypothesis generating is when there are findings that can be used for future hypotheses but should be interpreted with caution in the current results considering the effect of mass-significance.

7.1.2 RANDOM AND SYSTEMATIC ERRORS

Random errors such as unpredictable individual errors in the data entered in the registers should not represent any significant problems in this thesis because of the large cohorts and the random error should thus not be of significant overall impact on the results of this thesis. Systematic errors could occur, for example if the cutoff of detecting DM in the studies represented in this thesis are incorrectly set. However, the cutoffs in this thesis have been carefully evaluated and should not be a reason for systematic errors.

7.2 PAPER I-IV

The studies are limited in the amount and precision of data recorded in the data registers used and the number of CHD cases in the different cohorts in the studies are comparatively modest. In paper I-IV we did not have access to original medical records but since patients with CHD and/or T1DM are followed by subspecialized healthcare departments, the risk of misdiagnosing therefore should be low in these cases. However, patients with T2DM often get their diagnosis in primary care and there could be a risk of incorrect diagnoses in these individuals, but since we have defined T1DM and T2DM as explained in the method sections by ICD- codes, age and DM medication we have adjusted for this confounder and the risk for false positive T2DM diagnoses should be limited. The data

were available from the NPR, NDR and the CDR which are all large and well trusted registers which have almost complete coverage on diagnosis, hospitalisations, characteristics, morbidity and mortality and missing data are present in such a small extent it could be considered as a negligible source of bias [51, 129].

In paper I-IV data on several demographic details including educational level and other diseases were not retrieved, and this could be an epidemiological drawback and a methodological limitation. There is also a lack of more detailed information on the impact of prognostic factors associated with CHD.

7.2.1 PAPER I

A limitation in paper 1, was the lack of a control group with patients with CHD but without T2DM, which could limit the conclusions regarding the contributing effect of T2DM in a CHD population. The lesion classification of CHD, exercise capacity, number and complexity of previous surgeries, and general co-morbidities were not retrieved as an epidemiological drawback and a methodological limitation, which limits the conclusions regarding if the complexity of CHD contribute to T2DM. In the study, co-morbidities normally associated with CHD were not available in the dataset. Another limitation in the study was the limited number of patients with CHD and T2DM included in the cohort and a larger number would give more eligible results.

7.2.2 PAPER II

In paper II, access to a control group with CHD, but without T1DM was not available as an epidemiological drawback and a methodological limitation, which could limit the conclusions regarding the impact of T1DM in a CHD population. Due to a limited number of patients with CHD and T1DM, data on CHD lesion and classifications were not available but would be interesting to investigate further. Data were neither available on exercise capacity, or number and complexity of previous surgeries which limits the conclusions regarding contributing effect of how the complexity of CHD could contribute to T1DM. Missing data on e.g. year of onset of T1DM was a limitation in paper II as well as the number of potential matched controls, contributing to a relatively modest cohort in the end.

7.2.3 PAPER III

In paper III, missing data in the cohort due to a lack of diagnosis was to our knowledge limited or none because of the fact that if patients did not fulfil the matching criteria they were from the beginning excluded from the cohort database. However, there could be bias in terms of incorrectness of medical records or missing diagnosis in the original registers (type 1 or type 2 errors).

The patients in the cohort were not matched on any other co-morbidities since they were matched from birth.

In the large and trustful database that was used, a limitation could be the validity of CHD and T1DM diagnoses used as the base for the study as well as the registration of T1DM being a little more uncertain in the 1970s. In this study DM was defined as described in the method section, codes 250 (ICD-8 and ICD-9) or E10-14(ICD-10). Specific codes for T1DM and T2DM are not available for ICD-8 and 9. T1DM is in most scientific reports, epidemiologically defined as patients with only insulin therapy and onset age <30 years[51]. To adjust

for overestimation of T1DM and to distinguish patients with T1DM from those with T2DM in the NPR in this study, T1DM was defined as diagnosis of diabetes and onset age of diabetes ≤26 years, since drug administration data was not available and this cutoff is established in other large register studies. However, this classification is not always correct and T1DM onset can be found in older patients as well as the fact that younger patients can develop T2DM. However, T2DM is still extremely rare in Sweden at such young age while T1DM in older patients is uncommon and this potential data error could therefore be waived in our consideration.

The follow up time that was shorter in the second birth cohort compared to the first birth cohort could be considered as a limitation in the birth cohort study, which could limit the potential to assess differences by birth cohort.

Potentially important clinical variables, potential confounders, such as socioeconomic status, smoking, physical activity, causes of death and co-morbidities that may contribute to our understanding of the individual, patient-related risk was not investigated and would be valuable to be investigated further. Although, the socioeconomic status in this context for the Swedish population is less relevant because of overall small socioeconomic differences and a well-developed public health-care system. The matching in this cohort was also done by county to take in account this confounder, but there could still be some differences, and this would need to be studied further.

Considering that new onset T1DM is routinely managed in inpatient hospital care, it is unlikely that the fact that the study had no access to primary care data, have resulted in any missed diagnoses of T1DM from the population.

In the Cox multistate regression model that were used, the matching has at baseline been done by sex, year of birth and county. However, over time they diverse and over time as the patients receive T1DM they are compared separately but matched for gender through the whole multistate. Because of the unevenly distributed mortality in patients with CHD there is some uncertainty in the Cox multistate regression model that was used for analyses and the proportional hazard assumption was not met for transition state CHD to Death. The problem is due to a combination of the long-follow up study and the use of a matched control population with low mortality rate during childhood. The possibility to divide the follow-up time and perform separate analysis for each time period was not ideal because of few T1DM events (n=221) among patients with CHD. However, post hoc we did perform separate analysis for each time period which gave us similar results (Table 18). The large and significant difference of developing T1DM and the mortality after onset of T1DM in patients with CHD that is seen in the study is considered trustworthy and the result could not be waived because of this natural appearance with unevenly distributed data in the Cox multistate model.

7.2.4 PAPER IV

In paper IV, data were available from NPR and the Cause of Death Register which have almost complete coverage of all hospitalizations for CHD patients, matched by birth year and gender from a population-based control group without CHD. These registers have high validity and long follow-up making the registers particularly suitable for large-scale population-based research [129].

The cohort consisted of data from NPR, which was started in the 1960's. This means that patients in the first birth cohort, 1930-1959, needed to survive until at least 1960 to be included in the cohort, which could be considered a selection bias as CHD patients with non-complex CHD live longer. Also, a DM diagnosis before 1960 would not have been captured in the data and thus could have been categorized as DM onset after 35 years of age, for a patient being hospitalized after 1960, while the onset in actuality was before 35 year of age. Missing data in NPR should be considered as a selection bias, however after the 1980's the data variables used in the study were missing to such a small extent it could be considered as negligible size of bias. The data base that was used was a large trustful and reliable data base, stretching from 1960-2017. Since this is an epidemiologic retrospective register study, and although patients with CHD are followed by specialized care and the risk of misdiagnosing therefore should be low, the current study did not have access to original medical records. A limitation could therefore be the validity of diagnoses used as the base for the study as well as the registration of diagnosis being a little more uncertain in the 1960's. Still, this is large trustful epidemiological cohort study, covering the whole nation of Sweden , giving a broad knowledge about the whole CHD population and not only specialised inpatient care.

For ICD-10 specific codes for T2DM were available but for ICD-8 and 9 there are no specific codes for T2DM or T1DM. We chose to include all patients with first-onset diagnosis of DM after 35 years of age in ICD8, 9 and 10, potentially also including a small group of patients with T1DM. As described in earlier studies, Rawshani A et al. [66], T2DM makes up 93% of all patients with DM in Sweden and the inclusion of all patients with DM in our source cohort would then be a small source of selection bias although this was done for both patients with CHD and controls giving the same amount of bias. Another limitation is that the follow up time was shorter in the second compared to the first birth cohort, which could limit the potential to assess differences of DM and mortality by birth cohort. Potentially important clinical variables, such as socioeconomic status, smoking, physical activity, causes of death and co-morbidities that may contribute to our understanding of the individual, patient-related risk was not available.

8 CONCLUSION

8.1 CONCLUSION PAPER I-IV

The association between CHD and DM, T1DM and T2DM, including mortality and morbidity of DM, has not previously been investigated before in a large reliable cohort, representing prevalence on a national level. In conclusion, this thesis present data from nationwide registers showing a coexistence with a higher risk of DM in the CHD population, both T1DM and T2DM. This coexistence between CHD and DM was associated with increased mortality and morbidity. Suggesting the combination of CHD and DM to be more lethal than each diagnosis on its own, which has not been shown in large reliable national cohorts before.

8.1.1 PAPER I

The retrospective cohort design study in paper 1 described from a nationwide quality register, NDR, the development of T2DM in the adult CHD population with an estimated prevalence of between 4 and 8% and that CHD and secondary risk factors for cardiovascular disease frequently coexist. The overall mortality was 26.2% for CHD patients as compared with 19.9% for the control group, and five-year mortality rates were 5.2% for patients with CHD and T2DM compared to 3.4% in the controls. Treatment of conventional cardiovascular risk factors in patients with CHD could be considered important given the relatively high morbidity and high risk for mortality observed in patients with the combination of CHD and T2DM compared to controls with only T2DM. Early identification of unhealthy lifestyle factors and lifestyle advice is important for adult CHD patients, and routine screening with measurements of HbA1c, lipid levels and blood pressure may be considered appropriate for CHD patients with increasing age at specialized CHD units.

8.1.2 PAPER II

The retrospective cohort design study in paper II described a broad sample of patients from a nationwide quality register, NDR, of patients with T1DM.

Patients with CHD and T1DM had an earlier onset of diabetes, 13.9 vs. 17.4 years. The coexistence of CHD and T1DM was associated with significantly higher rates of microvascular complications, concurrent CVD, and mortality, 16 vs. 5% compared to controls with T1DM but without CHD. Patients with CHD and T1DM had a higher rate of co-morbidities, expressed as a higher number of hospitalizations per patient, 5.28 vs. 3.12, with a discharge diagnosis of CHD, IHD, HF, AF, stroke, PCI, CABG, or renal failure, after onset of T1DM compared with controls. The high mortality and morbidity among these patients merit further study and focused clinical attention.

8.1.3 PAPER III

In paper III, we described from a nationwide register (NPR) a cohort of patients with CHD

and population-based controls and showed a 50% higher incidence of developing T1DM and a 4-fold increased mortality risk after onset of T1DM in patients with CHD compared to controls without CHD. Suggesting the combination of CHD and T1DM to be more lethal than each diagnosis on its own. These findings are important in future medical care for patients with CHD.

8.1.4 PAPER IV

In paper IV, we described from a nationwide register (NPR) a nationwide cohort of mostly elderly patients with CHD and population-based controls without CHD, the risk of developing DM, consisting of at least 93% T2DM, was significantly higher in patients with CHD and was seen also if divided by birth cohort, gender or CHD lesion type. The risk of developing DM increased with severity of CHD compared to controls without CHD. The overall mortality was higher in patients with CHD after DM diagnosis compared to controls without CHD.

For detailed conclusion of paper IV, see Papers, paper IV.

8.1.5 SOME LAST WORDS

As the CHD population ages, the risk of developing diseases typically seen in the elderly increases. Patients with CHD are at least as prone to developing the metabolic syndrome and T2DM as the general population. At the same time the CHD population have co-morbidities which could contribute to an autoimmune response and T1DM. This thesis show that the CHD population do have a higher risk of T1DM and T2DM compared with the general population. Whether this is due to environmental risk factors or due to genetics needs to be further studied. Patients with CHD also have a higher mortality and morbidity after onset of DM compared with controls without CHD, indicating that the combination of CHD and DM are more lethal than each diagnosis on its own.

The growing numbers of adults with CHD will significantly affect cardiologist practise in the years to come, therefor these findings are important in future medical care for patients with CHD.

9 FUTURE PERSPECTIVES

The CHD population has increased worldwide due to better medical care and diagnostics and recent research indicates that the prevalence of people with CHD may be changing with higher prevalence numbers in the future. At the same time the elderly CHD population increases and with that the elderly populations diseases.

Although causality can never be proven in retrospective cohort studies, this thesis indicates that there is an association between CHD and DM. Patients with CHD have a higher risk of developing DM, T1DM and T2DM with a higher mortality and morbidity in patients with CHD and DM than either diagnosis on its own. Whether this is due to the lifestyle of these patients with a higher incidence of hospitalization, surgery and physical stress, trigging an autoimmune response with a result of T1DM or a more sedentary and unhealthier lifestyle resulting in T2DM or if there is a genetic link is not proven. Therefor it would be valuable and interesting to investigate further into more detailed information on the impact of lifestyle factors associated with CHD, such as exercise capacity, factors associated with the metabolic syndrome, socioeconomic background, education, number and complexity of previous surgeries which could contribute to our understanding about CHD and DM.

Speculatively, it would be valuable to investigate if a severe and complex CHD, resulting in hypoxia, could contribute to a pancreas insufficiency and DM in patients with CHD or if a genetic link could be detected. It would be valuable to investigate in larger cohorts divided by CHD lesion the outcome of T1DM, T2DM, mortality and morbidity. It would also be of great value to investigate the heredity, genetic markers and autoimmune antibodies for DM in patients with CHD.

Further, to investigate the autoimmune response, it would be valuable to in a future perspective investigate if there is an increased incidence of other autoimmune diseases in people with CHD. It is also of importance to investigate other confounding factors such as socioeconomic status, education level, smoking, alcohol and relevant medications. It could also be valuable and interesting to investigate maternity diabetes and the outcome of CHD and DM in the offspring.

However, all of this future research is of great importance to further understand the CHD population. Since it is still a relatively limited population, large reliable registers and cohorts are needed. Suggesting that Nordic or international cohorts and international cooperation may be required for a trustworthy research outcome of the incidence of DM (e.g. T1DM, T2DM, MODY, LADA), mortality, morbidity,

autoimmune antibodies and genetic markers for DM in patients with CHD compared with the general population without CHD.

In the future it is of great importance to maintain and improve the nationwide medical registers that are available in Sweden and thereby expand our knowledge and possibilities to analyze the number of outcomes in these registers. Observational studies and retrospective studies from nationwide registers are of great importance to evaluate the outcome since the whole population is studied which thereby limits the selection bias. It is of great importance to continue to evaluate the outcomes and treatments in both gender perspectives and by lesion to continue the improved clinical and medical care for the CHD population.

This thesis is a piece of trying to understand the CHD population and to improve and implement evidence-based knowledge in future medical care for these patients. The thesis is the first to show, using large and reliable national registers, that patient with CHD have a higher risk of developing DM, both T1DM and T2DM. The combination of having CHD and DM, T1DM or T2DM, are more lethal than either diagnosis on its own and are associated with more and difficult comorbidities than either diagnosis on its own. This is of great value for preventive, medical and diagnostic care for patients with CHD improving the longevity and quality of life in this population.

However, research is never definitive and is a continuously ongoing process where the scientific news of today is the history of tomorrow and I will myself do my very best to continue to be a part of this scientific development and future.

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11 REFERENCES

1. JM L. Dictionary of epidemiology. 4th ed. New York: Oxford University Press; 2001.

2. KJ R. Epidemiology: An introduction. USA: Oxford Press; 2002.

3. Susser M. Causal Thinking in the Health Sciences: Concepts and Strategies in Epidemiology. New York: Oxford University Press; 1973.

4. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J. 1950;2(4682):739-48.

5. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58:295-300.

6. Altman DG. Pratical statistics for medical research. London: Chapman & Hall/CRC; 2000.

7. 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.

8. 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. Scandinavian cardiovascular journal : SCJ. 2015;49(6):344-50.

9. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American College of Cardiology. 2002;39(12):1890-900.

10. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J. 2004;147(3):425-39.

11. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2095-128.

12. 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 internal medicine. 2017;177(2):224-30.

13. Michael A. Gatzoulis GDw, piers E.F. Daubeney. Diagnosis and Management of Adult Congenital Heart Diseases: Elsevier; 2018 1 march 2020.

14. Dastgiri S, Stone DH, Le-Ha C, Gilmour WH. Prevalence and secular trend of congenital anomalies in Glasgow, UK. Arch Dis Child. 2002;86(4):257-63.

15. Tagliabue G, Tessandori R, Caramaschi F, Fabiano S, Maghini A, Tittarelli A, et al. Descriptive epidemiology of selected birth defects, areas of Lombardy, Italy, 1999. Popul Health Metr. 2007;5:4.

16. Tan KH, Tan TY, Tan J, Tan I, Chew SK, Yeo GS. Birth defects in Singapore: 1994-2000. Singapore Med J. 2005;46(10):545-52.

17. Egbe A, Uppu S, Lee S, Stroustrup A, Ho D, Srivastava S. Temporal variation of birth prevalence of congenital heart disease in the United States. Congenit Heart Dis. 2015;10(1):43-50.

18. Leirgul E, Fomina T, Brodwall K, Greve G, Holmstrom H, Vollset SE, et al. Birth prevalence of congenital heart defects in Norway 1994-2009--a nationwide study. Am Heart J. 2014;168(6):956-64.

19. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide: A Systematic Review and Meta-Analysis. Journal of the American College of Cardiology. 2011;58(21):2241-7.

20. Collaborators GBDCHD. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc Health. 2020;4(3):185-200.

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

22. M. Dellborg JS. Medfödda hjärtfel hos vuxna - samlingsvolym2005 200508.

23. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth defects research Part A, Clinical and molecular teratology. 2007;79(10):714-27.

24. 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.

25. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014;130(9):749-56.

26. 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.

27. 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 research Part A, Clinical and molecular teratology. 2007;79(10):714-27.

28. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation. 2010;122(22):2264-72.

29. Hook EB. Incidence and prevalence as measures of the frequency of birth defects. American journal of epidemiology. 1982;116(5):743-7.

30. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241-7.

31. Bradbury J. Deaths from congenital heart defects decrease in USA. Lancet (London, England). 2001;357(9268):1595.

32. 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.

33. Eskedal L, Hagemo PS, Eskild A, Aamodt G, Seiler KS, Thaulow E. Survival after surgery for congenital heart defects: does reduced early mortality predict improved long-term survival? Acta paediatrica (Oslo, Norway : 1992). 2005;94(4):438-43.

34. 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.

35. Morris CD, Menashe VD. 25-year mortality after surgical repair of congenital heart defect in childhood. A population-based cohort study. Jama. 1991;266(24):3447-52.

36. Nieminen HP, Jokinen EV, Sairanen HI. Late results of pediatric cardiac surgery in Finland: a population-based study with 96% follow-up. Circulation. 2001;104(5):570-5.

37. The L. Growing older with congenital heart disease. Lancet (London, England). 2015;385(9979):1698.

38. Mikael Dellborg JS. Medfödda hjärtfel hos vuxna -samlingsvolym2005.

39. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. European heart journal. 2010;31(10):1220-9.

40. Engelings CC, Helm PC, Abdul-Khaliq H, Asfour B, Bauer UM, Baumgartner H, et al. Cause of death in adults with congenital heart disease - An analysis of the German National Register for Congenital Heart Defects. Int J Cardiol. 2016;211:31-6.

41. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, van den Merkhof LF, Baur LH, et al. Circumstances of death in adult congenital heart disease. Int J Cardiol. 2012;154(2):168-72.

42. Mandalenakis Z, Karazisi C, Skoglund K, Rosengren A, Lappas G, Eriksson P, et al. Risk of Cancer Among Children and Young Adults With Congenital Heart Disease Compared With Healthy Controls. JAMA Netw Open. 2019;2(7):e196762.

43. 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.

44. 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. 2018;137(9):928-37.

45. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Hansson PO, Dellborg M. Ischemic Stroke in Children and Young Adults With Congenital Heart Disease. Journal of the American Heart Association. 2016;5(2).

46. SWEDCON. The Swedish Registry of Congenital Heart Disease. https://www.ucr.uu.se/swedcon/; 2020 1 march 2020.

47. Organization WH. Global reports on diabetes. https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=21162FE107C7A821131D44898419C4AA?sequence=1; 2018 1 Jan 2020.

48. Federation ID. IDF Diabetes Atlas. https://diabetesatlas.org/en/; 2020 1 March 2020.

49. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine. 1998;15(7):539-53.

50. Läkemedelsverket. Läkemedelsboken. https://lakemedelsboken.se/kapitel/endokrinologi/diabetes_mellitus.html0p 2019.

51. S G, A. Svensson, B. Eliasson, K. E-Oloffson, S. Björck, E. linder, P. Samuelsson, M. Miftaraj, I. Almskog. NDR Year Report. https://www.ndr.nu/#/arsrapport; 2018 12 Dec 2019.

52. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. Bmj. 2004;328(7442):750-4.

53. Maahs DM, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, et al. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2014;130(17):1532-58.

54. Patricia Jackson Allen (Editor) JAVE NASE. Primary Care of the Child with a Chronic Condition2009.

55. Diaz-Valencia PA, Bougneres P, Valleron AJ. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. BMC public health. 2015;15:255.

56. Rawshani A, Landin-Olsson M, Svensson AM, Nystrom L, Arnqvist HJ, Bolinder J, et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia. 2014;57(7):1375-81.

57. Svensson A-M GrtS, Samuelsson P, Miftaraj M, Eliasson B, Cederholm J, Rawshani A. The Swedish National Diabetes Register. https://http://www.ndr.nu/pdfs/20 years of successful improvements_lowres_singelpage.pdf.: The Swedish National Diabetes Register; 2016 1 June 2016.

58. Ludvigsson J. Increasing Incidence but Decreasing Awareness of Type 1 Diabetes in Sweden. Diabetes Care. 2017;40(10):e143-e4.

59. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. Jama. 2014;311(17):1778-86.

60. Ahadi M, Tabatabaeiyan M, Moazzami K. Association between environmental factors and risk of type 1 diabetes - A case-control study. Endokrynologia Polska. 2011;62(2):134-7.

61. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615-25.

62. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. Jama. 2002;287(19):2570-81.

63. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. European heart journal. 2013;34(31):2444-52.

64. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. European heart journal. 2013;34(31):2436-43.

65. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia. 2006;49(4):660-6.

66. Rawshani A, Rawshani A, Gudbjornsdottir S. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med. 2017;377(3):300-1.

67. Ritsinger V, Hero C, Svensson AM, Saleh N, Lagerqvist B, Eeg-Olofsson K, et al. Mortality and extent of coronary artery disease in 2776 patients with type 1 diabetes undergoing coronary angiography: A nationwide study. Eur J Prev Cardiol. 2017;24(8):848-57.

68. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet (London, England). 2005;365(9467):1333-46.

69. NDR. NDR Årsrapport. https://ndr.nu/pdf/Arsrapport_NDR_2014.pdf; 2014.

70. Jansson SP, Fall K, Brus O, Magnuson A, Wandell P, Ostgren CJ, et al. Prevalence and incidence of diabetes mellitus: a nationwide population-based pharmaco-epidemiological study in Sweden. Diabet Med. 2015;32(10):1319-28.

71. Ravi V, Pulipati P, Vij A, Kodumuri V. Meta-Analysis Comparing Double Versus Triple Antithrombotic Therapy in Patients With Atrial Fibrillation and Coronary Artery Disease. Am J Cardiol. 2020;125(1):19-28.

72. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Response by Kosiborod et al to Letters Regarding Article, "Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)". Circulation. 2018;137(9):989-91.

73. Frias JP, Nauck MA, Van J, Benson C, Bray R, Cui X, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: A 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. Diabetes Obes Metab. 2020.

74. Norhammar A, Mellbin L, Cosentino F. Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor. Eur J Prev Cardiol. 2017;24(3_suppl):52-60.

75. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. Jama. 2003;289(1):76-9.

76. Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men. A general population study. Diabetes Care. 1998;21(4):539-45.

77. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. Diabet Med. 2006;23(5):516-21.

78. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB, Sr., et al. Trends in cardiovascular complications of diabetes. Jama. 2004;292(20):2495-9.

79. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007;356(23):2388-98.

80. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ. 2005;331(7517):614.

81. Rawshani A, Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-44.

82. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet (London, England). 2007;369(9563):750-6.

83. Johansson I, Edner M, Dahlstrom U, Nasman P, Ryden L, Norhammar A. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. Eur J Heart Fail. 2014;16(4):409-18.

84. Johansson I, Dahlstrom U, Edner M, Nasman P, Ryden L, Norhammar A. Prognostic Implications of Type 2 Diabetes Mellitus in Ischemic and Nonischemic Heart Failure. Journal of the American College of Cardiology. 2016;68(13):1404-16.

85. Ahadi M, Tabatabaeiyan M, Moazzami K. Association between environmental factors and risk of type 1 diabetes - a case-control study. Endokrynologia Polska. 2011;62(2):134-7.

86. McNally JD, O'Hearn K, Lawson ML, Maharajh G, Geier P, Weiler H, et al. Prevention of vitamin D deficiency in children following cardiac surgery: study protocol for a randomized controlled trial. Trials. 2015;16:402.

87. Brix-Christensen V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. Acta anaesthesiologica Scandinavica. 2001;45(6):671-9.

88. Gazit AZ, Huddleston CB, Checchia PA, Fehr J, Pezzella AT. Care of the pediatric cardiac surgery patient--part 1. Current problems in surgery. 2010;47(3):185-250.

89. McEwan A. Aspects of bleeding after cardiac surgery in children. Paediatric anaesthesia. 2007;17(12):1126-33.

90. 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.

91. 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.

92. SCB. Personal Identity Number https://www.scb.se2012 [

93. SCB http://www.scb.se/BE0101 SCB; 2012 [updated 120331. Available from: http://www.scb.se/BE0101

94. Gudbjornsdottir S, Cederholm J, Nilsson PM, Eliasson B, Steering Committee of the Swedish National Diabetes R. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care. 2003;26(4):1270-6.

95. Gudbjornsdottir S. Nationella diabetesregistrets årsrapport https://www.ndr.nu/#/arsrapport2005 [

96. Welfare NBoHa. The Cause of Death Registry https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/2019 [

97. SCB. the Registry of Total Population https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-totalbefolkningen-rtb/2020 [

98. SWEDCON. The Swedish Registry of Congenital Heart Disease - The Annual Report https://www.ucr.uu.se/swedcon/: SWEDCON; 2018 [

99. -STROBE UoB. STROBE statement https://www.strobe-statement.org2009 [

100. WHO. ICD purpose and uses https://www.who.int/classifications/icd/en/2019 [

101. Health TNBo. The classification ICD-10 https://www.socialstyrelsen.se/utveckla-verksamhet/e-halsa/klassificering-och-koder/icd-10/: The National Board of Health; 2019 [

102. Population Statistic http://www.scb.se/BE0101: SCB; 2018 [

103. Swedcon. http://www.ucr.uu.se/swedcon/index.php/arsrapporter2015 [

104. RC T. R: A language and environment for statistical computing. 2017.

105. Authority SER. Swedish Ethical Review Authority https://etikprovningsmyndigheten.se2020 [

106. Welfare NBoHa. National Board of Health and Welfare. http://www.socialstyrelsen.se/statistics National Board of Health and Welfare; 2018 20181201.

107. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.

108. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94(3):311-21.

109. 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.

110. 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. Am J Cardiol. 2009;103(10):1445-50.

111. 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.

112. 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. Am J Cardiol. 2012;109(11):1657-63.

113. Zethelius B, Gudbjornsdottir S, Eliasson B, Eeg-Olofsson K, Cederholm J, Swedish National Diabetes R. Level of physical activity associated with risk of cardiovascular diseases and mortality in patients with type-2 diabetes: report from the Swedish National Diabetes Register. Eur J Prev Cardiol. 2014;21(2):244-51.

114. Zaidi AN, Bauer JA, Michalsky MP, Olshove V, Boettner B, Phillips A, et al. The impact of obesity on early postoperative outcomes in adults with congenital heart disease. Congenit Heart Dis. 2011;6(3):241-6.

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

116. Butalia S, Leung AA, Ghali WA, Rabi DM. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovasc Diabetol. 2011;10:25.

117. Schnell O, Erbach M, Hummel M. Primary and secondary prevention of cardiovascular disease in diabetes with aspirin. Diab Vasc Dis Res. 2012;9(4):245-55.

118. Ferranti SDd, Ian H dB, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 Diabtes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37:2843-63.

119. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008;117(18):2320-8.

120. Madsen NL, Goldstein SL, Froslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int. 2017;92(3):751-6.

121. 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. Cardiology in the young. 2017:1-8.

122. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37(10):2843-63.

123. Madsen NL, Marino BS, Woo JG, Thomsen RW, Videbœk 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. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2016;5(7):e003076.

124. Lerman JB, Parness IA, Shenoy RU. Body Weights in Adults With Congenital Heart Disease and the Obesity Frequency. Am J Cardiol. 2017;119(4):638-42.

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

126. 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. Int J Cardiol. 2015;187:219-26.

127. 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. Int J Cardiol. 2020.

128. Strain WD, Paldanius PM. Diabetes, cardiovascular disease and the microcirculation. Cardiovasc Diabetol. 2018;17(1):57.

129. 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.

12 APPENDIX

APPENDIX A. STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
INTRODUCTION		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
METHODS		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed
		(e) Describe any sensitivity analyses

APPENDIX A (CONTINUED). STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

APPENDIX B. Congenital Heart Disease and Other Diagnosis of Importance in This Thesis According to the International Classification of Diseases and Related Health Problems

Diagnosis	ICD-8	ICD-9*	ICD-10
Tetralogy of Fallot	746.29	745C	Q21.3
Transposition of the great vessels	746.1	745B	Q20.3
Common arterial trunk	746.0	745A	Q20.0
Ventricular septal defect	746.39	745E	Q21.0
Atrial septal defect or patent foramen ovale	746.4	745F	Q21.1
Congenital tricuspid stenosis or atresia	746.54	746B	Q22.4
Ebstein's anomaly	746.54	746C	Q22.5
Congenital stenosis of the aortic valve	746.73	746D	Q23.0
Congenital insufficiency of the aortic valve	746.79	746E	Q23.1
Congenital mitral stenosis	746.59	746F	Q23.2
Congenital mitral insufficiency	746.59	746G	Q23.3
Hypoplastic left heart syndrome	746.74	746H	Q23.4
Congenital subaortic stenosis	746.79	746W	Q24.4
Cor triatriatum	746.82	746W	Q24.2
Infundibular pulmonic stenosis	746.63	746W	Q24.3
Congenital coronary vessel anomalies	746.85	746W	Q24.5
Congenital heart block	746.86	746W	Q24.6
Coarctation of the aorta	747.19	747B	Q25.1
Interruption of the aortic arch (atresia or stenosis of the aorta)	747.19	747B	Q25.2, Q25.3
Other unspecified congenital malformations of the aorta	747.29	747C	Q25.4, Q25.8, Q25.9
Congenital malformations of the pulmonary artery	747.34, 747.39	747D	Q25.5–Q25.7
Congenital malformations of the great veins	747.49, 747.59	747E	Q26
Cor biloculare	746.89	745H	Q20.8
Double outlet right ventricle	746.19	745B	Q20.1
Double outlet left ventricle	746.19	745B	Q20.2
Double inlet ventricle	746.37	745D	Q20.4
Discordant atrioventricular connection	746.19	745B	Q20.5
Isomerism of atrial appendages	745.89	745W	Q20.6
Unspecified congenital malformations of the cardiac chambers	746.89	746X	Q20.8, Q20.9
Atrioventricular septal defect	746.47	745G	Q21.2
Aortopulmonary septum defect	746.09	745W	Q21.4
Other congenital malformations of the cardiac septum	745.89	745W	Q21.8
Unspecified congenital malformations of the cardiac septum	745.99	745X	Q21.9
Pulmonary valve atresia	746.64	746A	Q22.0
Congenital stenosis of the pulmonary valve	746.63	746A	Q22.1

APPENDIX B (CONTINUED). Congenital Heart Disease and Other Diagnosis of Importance in This Thesis According to the International Classification of Diseases and Related Health Problems

Diagnosis	ICD-8	ICD-9*	ICD-10
Congenital pulmonary valve insufficiency	746.69	746A	Q22.2
Other congenital malformations of the pulmonary valve	746.00	746A	Q22.3
Hypoplastic right heart syndrome	746.69	746B	Q22.6
Other congenital malformations of the tricuspid valve	746.54	746B	Q22.8, Q22.9
Other congenital malformations of aortic and mitral valves	746.89	746W	Q23.8, Q23.9
Congenital phlebectasia	747.89	747G	Q27.4
Other specified congenital malformations of the heart	746.89	746W	Q24.8
Unspecified congenital malformations of the heart	746.84	746X	Q24.9
Patent ductus arteriosus	747.0	747A	Q25.0
Unspecified congenital malformations of the circulation	747.9	747X	Q28.9
Sequestration of the lungs	748.5	748F	Q33.2
Secondary hypertension	405	405	I15.8, I15.9
Vitium organicum cordis (VOC)	-	-	I33–37
Myocardial infarction	410	410	I21
Hypertension	400-404	401-405	I10-I15
Diabetes mellitus	250	250	E10-E14
Atrial fibrillation	427,92	427D	I48
Ischemic stroke	433-434	434-436	I63-I64
Heart failure	427	428	I50
Hyperlipidemi	272,00-272,01	272A,272E	E780,E782,E784,E785
CVD	404-408	405-409	I0-I9