International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital heart defect – A nationwide cohort study☆

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ARTICLE INFO

Article history:
Received 14 July 2019
Received in revised form 27 November 2019
Accepted 8 January 2020
Available online xxxx

Keywords:
CHD
Diabetes
T1DM
Mortality

ABSTRACT

Background: 1% of all live born children are born with a congenital heart defect (CHD) and currently 95% reach adulthood. Type 1 diabetes mellitus (T1DM) is an autoimmune disease that can develop due to i.e. heredity, exposure to infections and stress-strain. The incidence of T1DM in patients with CHD is unknown and we analysed the risk of developing T1DM for patients with CHD, and how this influences mortality.
Methods: By combining registries, the incidence of T1DM and the mortality was analysed in patients with CHD by birth cohort (1970–1993, 1970–1984 and 1984–1993) matched with population-based controls matched for sex, county and year of birth without CHD and followed from birth until a maximum of 42 years.
Results: 221 patients with T1DM among 21,982 patients with CHD and 1553 patients with T1DM among 219,816 matched controls were identified. The hazard ratio (HR) for developing T1DM was 1.50 (95%, CI 1.31–1.73) in patients with CHD compared to the controls and the first birth cohort (1970–1984) had the highest risk for T1DM, HR 1.87 (95%, CI 1.56–2.24). After onset, mortality risk was 4.21 times higher (95%, CI 2.40–7.37) in patients with CHD and T1DM compared to controls with T1DM.
Conclusion: From a nationwide cohort of patients with CHD and controls, the incidence of developing T1DM was 50% higher in patients with CHD, showing a significant increase in risk among birth cohort 1970–1984. The combination of CHD and T1DM was associated with a 4-fold increase in mortality compared to controls with only T1DM.

1. Background

Congenital heart defect (CHD) is the most common congenital malformation among live born children as well as a major cause of death during infancy and young children [1–6]. Globally about 1% of all live born children are diagnosed with CHD [3,4,7–9]. With improved clinical, medical and surgical care, survival rates have improved to the point that >95% of children with CHD now reach adulthood [1,3,4,6,7,9–19]. Diabetes mellitus type 1 (T1DM) is considered to be caused by an autoimmune reaction where the body's immune system attacks insulin-producing cells [20,21] with an increased risk of cardiovascular disease and mortality [22]. T1DM is one of the most common chronic diseases during childhood [23]. The incidence of T1DM varies by country [21]. In Sweden, the annual incidence of T1DM among people aged younger than 25 years is approximately 40/100000 person years which give a prevalence of 1% [24–26]. In the US the prevalence has been reported to be increasing and was approaching 2% in 2009 [27].

Increased exposure to infections, lifestyle changes, and increased biologic stress-strain could contribute to an increased risk of developing T1DM [28]. Patients with CHD may be more likely to be exposed to infection, lifestyle changes and other biological stressors or strain due to early surgery and repeat hospitalizations [29–32] and therefore potentially have an increased risk of developing T1DM. The effect on mortality of T1DM in patients with CHD has not been reported over long term or in large numbers but the co-occurrence may potentially have a significant effect on mortality.

We have previously described a relationship between CHD and T1DM in a large registry of diabetes where patients with CHD were shown to have an earlier onset of T1DM and a higher mortality [33]. However, that study did not include a control group with CHD without diabetes. Therefore, the current study compares, in a larger cohort, the incidence of T1DM and the mortality in patients with CHD, with CHD and diabetes and matched controls.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2020.01.010
0167-5273/

2. Methods

2.1. Study design

We performed a cohort study that described the incidence of T1DM and the mortality in adult patients with CHD before and after onset of T1DM divided by birth cohort, all (born 1970–1993), first birth cohort (born1970–1984), second birth cohort (born1985–1993), compared to population-based controls matched for sex, year of birth and county without CHD and followed from birth until a maximum of 42 years, 1970–2011.

2.2. Data sources

The computations for this study are based on individual data from the Swedish registries 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 National Board of Health and Welfare pending approval by the appropriate ethics committee [34], and the Board can also provide information about the registry and persons to contact for queries. All relevant aggregated data on number of cases and controls are already contained within the article, its supporting information files, and its supporting information.

Swedish hospitals are publicly financed and offer care at low cost to Swedish adult citizens and free to children. The Swedish National Patient Registry was started 1964 and includes statistics of diseases and surgical treatment of patients in Sweden. From 1987 all Swedish hospitals are required to report principal and contributory discharge diagnoses, and surgical procedures to the National Patient registry. From 2001, the registry also includes all outpatient hospital visits, including day surgery and psychiatric care from private and public caregivers.

From 1961, all deaths are reported in the Cause of Death Registry. The six cardiothoracic surgery clinics in Sweden have registered all procedures and hospitalizations since 1970. For this study, all data were obtained from the Inpatient, Outpatient, and Cause-of- Death Registries and linked through the unique Swedish 10-digit personal identity number (PIN), which enables each person to be followed over time. The PIN system (currently 12 digits) was introduced in 1947 and is based on date of birth, sex and until 1990 region of birth. Inpatient data reported has a drop-off of about 1% for the most frequently used variables. The main diagnosis is missing for about 1% of all care cases in 1988–2016. The PIN is missing or incorrect in 1.6% of all care cases in 1988–2016, the majority of which relates to children born abroad. The loss of birth year, which is of importance in our cohort is 0.1%. The variables hospital, clinic, gender, enrollment and discharge date have a negligible degree of missing data. The rate of missing data in the specialized outpatient care has decrease in recent years and was approximately 1% in 2018 [35].

2.3. Classification of diagnosis

Patients with CHD are diagnosed in standardized clinical practice and clinical consensus by boarded specialist in cardiology. Patients with T1DM are diagnosed in standardized clinical practice by blood sample and clinical consensus are followed by boarded physicians in hospital. Patients with CHD and patients with T1DM in the data base have been followed by boarded specialists of cardiology and/or endocrinology.

All discharge and hospital visit diagnoses were coded according to the International Classification of Disease (ICD) system. The ICD Eighth Revision (ICD-8) was used from 1968 to 1986, ICD-9 from 1987 to 1996, and ICD-10 from 1996 onwards [36]. A more detailed description of the study population has previously been published [4]. In brief, all men and women born between January 1970 and December 1993 who had a diagnosis of CHD by a licensed physician and were registered in the Inpatient, Outpatient, or Cause-of-Death Registry were included. Follow-up data and mortality were collected until December 2011.

CHD was defined according to the ICD-8 codes 745-747, ICD-9 codes 745-747 and ICD-10 codes Q20–25 codes and by at least one outpatient visit, hospitalization, or death certificate due to CHD ICD code (Appendix A). Diabetes mellitus was defined as codes 250 (ICD8 and ICD-9) or E10-14(ICD-10). To distinguish patients with T1DM from those with type 2 diabetes mellitus (T2DM) and to avoid overestimation of T2DM in the National Patient Registry, T1DM was defined as diagnosis of diabetes and onset age of diabetes ≤26 years in the study. Data was linked between the National patient registry and the Swedish Cause-of-Death Registry by the PIN. Information on date and cause of death was collected from the Cause-of-Death Registry.

2.4. Subjects

For patients with CHD, information was retrieved from the National Patient Registry. For each CHD patient, 10 control individuals without a diagnosis of CHD or diabetes were randomly selected from the Total Population Registry in Sweden, matched by year of birth, sex, and county. However, a total of 14 patients could only be matched by 9 controls each. The hierarchic classification was used for CHD stratification [34] (Appendix B).

To compare the mortality for patients with CHD and T1DM, both patients with CHD and controls were studied after onset of T1DM.

2.5. Statistical analysis

Baseline characteristics are presented as numbers and proportions for each lesion types by cases and controls separately. For continuous variables the mean follow-up time and standard deviation was reported. 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 100-person-years and reported separately by birth-cohorts (1970–1993, 1970–1984 and 1985–1993).

To investigate the risk of diabetes among patients with CHD and controls, 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 (Appendix C). A transition from one health state to another occurs by an event (diabetes or death). The follow-up time was until first occurrence of hospitalization of 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 but over time they diverse and over time as the patients receive T1DM they are compared separately. Although they are still matched for gender 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.

All statistical analyses and data processing were performed with R software, Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [37]. The “mstate” package was used to fit the multi-state model.

2.6. Ethics

The PIN for each patient in the National Patient Registry 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 this study could not be provided and was therefore waived. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Regional Ethical Review Board in Gothenburg, Sweden.

Please cite this article as: A. Björk, Z. Mandalenakis, K.W. Giang, et al., Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital hear..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.01.010

3. Results

3.1. Baseline characteristics

From the National Patient Registry 21,982 patients with CHD were identified, 51.5% men and 48.5% women. 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 controls. 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 1, Appendix D, Appendix E).

3.2. The incidence of T1DM

Of patients with CHD, 221 (1%) adults were diagnosed with T1DM, compared to 1553 (0.7%) of the controls. The incidence rate of T1DM was higher among patients with CHD, 3.7 vs 2.5/10,000 person-years among controls and with an HR of 1.50 (95% CI 1.3–1.73) (Fig. 1, Tables 2 and 3). In overall, the risk of T1DM was increased throughout the study in patients with CHD compared to controls (Fig. 1, Table 2).

In the first birth cohort the risk of T1DM was higher among patients with CHD compared to the matched controls with an incidence rate of 3.7 vs 2.0 T1DM per 10,000 person-years. The relative risk among CHD patients was almost twice that of the controls, (HR 1.9, 95% CI 1.55–2.24, Tables 2, 3, Fig. 1). In the second birth cohort the difference in incidence was numerically smaller and not statistically significant (HR 1.14, 95% CI 0.9–1.41, Table 2, Fig. 1). The cumulative probability of diabetes by birth cohort during the up to 42 years follow up period is shown in Fig. 1.

3.3. Mortality

The mortality risk was 16 times higher in patients with CHD compared to the controls (HR 16.19, 95% CI 15.00–17.48, Table 3, Fig. 1). After onset of T1DM, the total mortality among patients with CHD was four times higher, compared to controls (HR 4.21, 95% CI 2.40–7.37, Tables 2, 3, Fig. 1) and with a mortality rate of 2414 vs 543/10,000 person years, respectively.

Table 1
Baseline characteristics of the study population by CHD and controls divided by birth cohort and lesion group.

	Case	Control	P
	(*N* = 21,982)	(*N* = 219,816)	
Gender			>0.999
Men	11,331 (51.5%)	113,319 (51.6%)	
Women	10,650 (48.5%)	106,497 (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%)	17,499 (8.0%)	
Yes	20,139 (91.6%)	202,317 (92.0%)	
Birth cohort			>0.999
1970–1984	11,508 (52.4%)	115,079 (52.4%)	
Age at end of study	32.2 ± 8.7	34.4 ± 4.5	<0.001
1985–1993	10,474 (47.6%)	104,737 (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%)	24,049 (10.9%)	
CoA	1306 (5.9%)	13,060 (5.9%)	
Conotruncal defects	2022 (9.2%)	20,230 (9.2%)	
Other	10,793 (49.1%)	107,918 (49.1%)	
Severe non-conotruncal defects	1087 (4.9%)	10,870 (4.9%)	
VSD	4369 (19.9%)	43,689 (19.9%)	
Lesion by severity			0.993
Complex	4415 (20.1%)	44,160 (20.1%)	
Non-Complex	17,567 (79.9%)	175,656 (79.9%)	

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

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 (HR 4.06, 95%CI 2.21–7.47, Tables 2, 3) and 5 times higher in the second birth cohort, (HR 5.18, 95%CI 1.24–21.72, Tables 2, 3), with a mortality rate of 80 vs 20 and 33.3 vs 6.3/10,000 person-years, respectively. The cumulative probability of mortality by birth cohort during the 42-year follow up period is shown in Fig. 1.

4. Discussion

4.1. The incidence of T1DM

The incidence of T1DM in CHD patients compared to healthy controls has not been extensively studied before. In the present study, patients with CHD had an almost 50% higher incidence of T1DM compared to patients without CHD, in line with our previous data [33].This is the first time an increased incidence of T1DM has been reported for patients with CHD. However, a Danish registry study reported the relative risk of developing T2DM to be 1.4 for patients with CHD above 30 years of age [38]. The increased risk of developing T1DM in patients with CHD could be due to increased physical and mental stress in patients with CHD, as well as more illnesses and hospitalizations or it could be caused by genetics predisposing for both CHD and T1DM. Although this is purely speculative, this 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. This, however, was not possible in the present cohort, while the number with specific CHD diagnoses and T1DM was limited.

In this large registry study, the increased risk of developing T1DM was primarily seen among patients with CHD from the first birth cohort, born between 1970 and 1984. However, in the second birth cohort this risk was numerically smaller and not statistically significant. We have no clear explanation for this finding but 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. It 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. The registration of T1DM may potentially been less accurate for controls than for CHD patients in the earliest cohort and the relative increase among controls in incidence of T1DM in the later cohort may at least partially be an effect of better registration.

4.2. Mortality

In the present study, the mortality was 16 times increased in patients with CHD compared to the controls, which is line with earlier studies [6]. However, an association of diabetes, CHD and mortality has been observed by some authors. In a large registry study from Germany, diabetes was a non-significant risk factor for death among 2596 adult patients with CHD, mean age 33–39 [39]. In the present study, the mortality was increased in patients with T1DM and CHD 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 acute and early complications, which is in line with previous studies [2,33].

The increased mortality in patients with T1DM and CHD seems mostly related to the presence of CHD itself, although our data indicate that the combination of T1DM and CHD is associated with higher mortality than either disease alone, which is in line with earlier studies presenting that patients with T1DM have higher mortality due to a higher risk of cardiovascular disease [40].

Please cite this article as: A. Björk, Z. Mandalenakis, K.W. Giang, et al., Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital hear..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.01.010

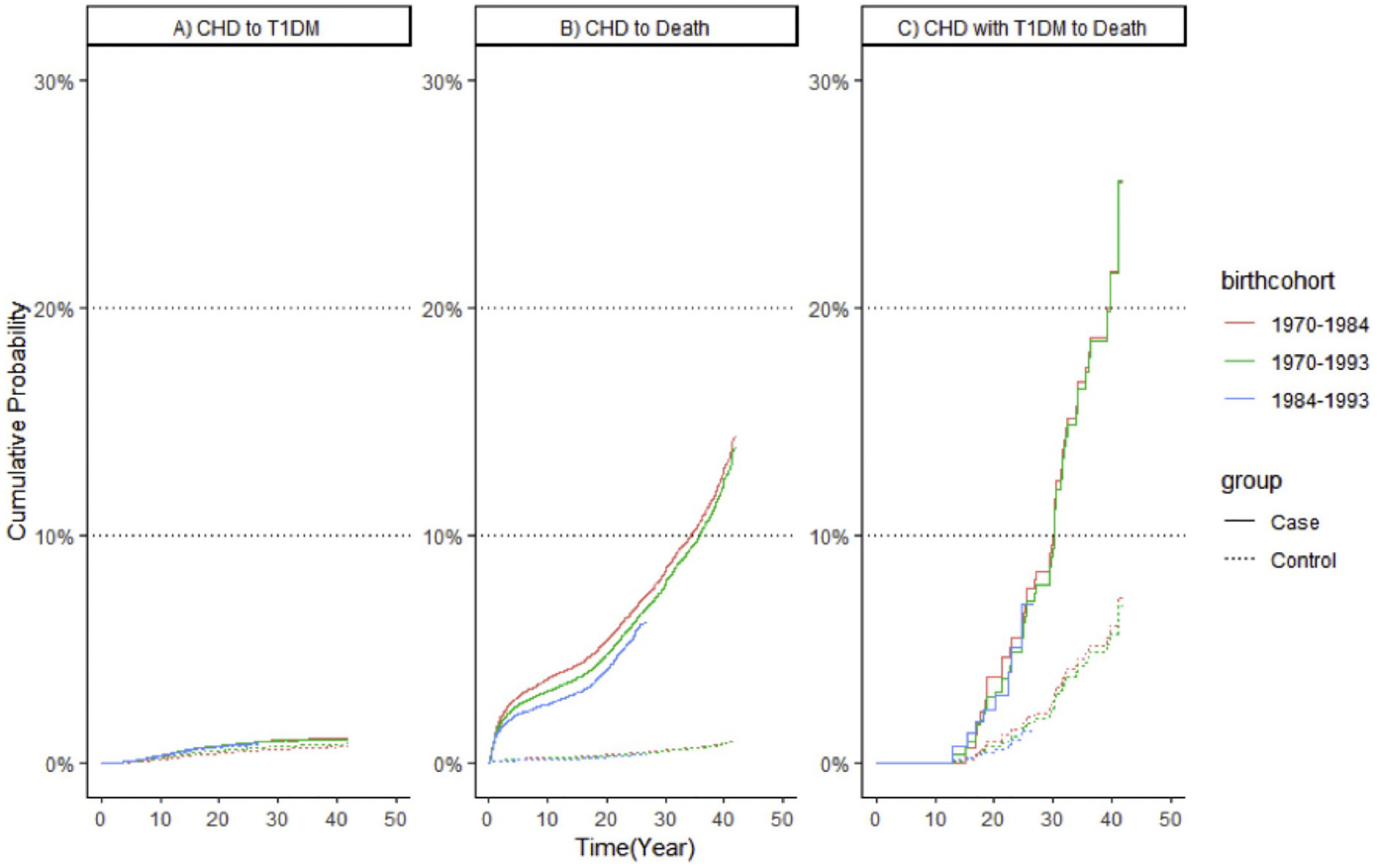

Fig. 1. The cumulative probability of diabetes mellitus type 1 (T1DM) and death by birth cohort. In a multistate cox regression model, patients with congenital heart defect (CHD) had an higher cumulative probability of developing T1DM in both birth cohort groups compared to the controls. Patients with 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.

4.3. Limitations

In the retrospective cohort design study, data were available from the National Patient Registry and the Cause-Of-Death Registry which have almost complete coverage of all hospitalizations for CHD patients matched by a control group matched by birth year, gender and county [41]. Since the patients were matched from birth we did not match on any other co-morbidities. There were no missing data in the cohort because if the patients did not fulfill the matching criteria or did not have a diagnosis they were not included in the database from the beginning. The cohort consisted of data from National Patient Registry and missing data could be considered as a selection bias, however since 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, stretched from 1970 to 2011.Since this is an epidemiological register study, and although patients with CHD are followed by special 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 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 70s. In this study diabetes mellitus was defined as codes 250 (ICD-8 and ICD-9) or E10-14(ICD-10) described in the method section. To distinguish patients with T1DM from those with T2DM in the National Patient Registry and to adjust for overestimation of T1DM, T1DM was defined as diagnosis of diabetes and onset age of diabetes ≤26 years in the study. For ICD-8 and 9 there are no specific codes for T1DM or T2DM. We choose the age <26 while this cutoff is established

Table 2
Incidence rate of diabetes mellitus type 1 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 toT1DM	Case	221	590,716.5	3.7(3.3–4.3)	137	367,861.0	3.7(3.1–4.4)	84	222,855.5	3.8(3.0–4.7)
	Control	1553	6,251,627.6	2.5(2.4–2.6)	785	3,940,993.7	2.0(1.9–2.1)	768	2,310,633.8	3.3(3.1–3.6)
CHD to death	Case	1654	590,716.5	28.0(26.7–29.4)	1157	367,861.0	31.5(29.7–33.3)	497	222,855.5	22.3(20.4–24.4)
	Control	1080	6,251,627.6	1.7(1.6–1.8)	766	3,940,993.7	1.9(1.8–2.1)	314	2,310,633.8	1.4(1.2–1.5)
T1DM to death	Case	20	3025.9	66.1(40.4–102.1)	17	2123.7	80.0(46.6–128.2)	3	902.2	33.3(6.9–97.2)
	Control	32	21,514.0	14.9(10.2–21.0)	27	13,533.0	20.0(13.1–29.0)	5	7981.1	6.3(2.0–14.6)

CHD = congenital heart disease, pyrs = person-years, T1DM = type-1 diabetes mellitus, IR = incidence rate/10^4 pyrs, CI = confidence interval.

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Table 3
Risk of diabetes mellitus type 1 and mortality among patients with CHD by birth cohort.

	All		1970–1984		1984–1993	
	[a]HR (95% CI)	p-Value	[a]HR (95% CI)	p-Value	[a]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)	0.27
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)	0.025

CHD = congenital heart disease, T1DM = diabetes mellitus type 1, HR = hazard ratio, CI = confidence interval, reference = control, reference = control with no CHD.
[a] Adjusted for gender.

in other large registry studies to ensure that we did not overestimate the amount of patients with T1DM and that all of the patients that were found in the cohort had T1DM and not T2DM, since T2DM is still extremely rare in Sweden at such young age. Patients can get T1DM in older age but this is also very uncommon and could therefore be waived in our consideration.

Another limitation in the birth cohort study is the follow up time that was shorter in the second birth cohort compared to the first birth cohort, which could limit the potential to assess differences 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 were not investigated and would be valuable to be investigated further as well as the differences regarding severity classification of CHD by lesion. However, 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. We have also matched the cohort by county to take in account this cofounder, but there could still be some differences and this would need to be studied further.

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

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

5. Conclusion

From a nationwide cohort of patients with CHD and controls, the risk of developing T1DM was 50% higher in patients with CHD and the mortality after onset of T1DM was associated with a 4-fold increase in patients with CHD compared to controls without CHD. This study suggests 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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.01.010.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by a grant from the Swedish Heart-Lung Foundation (20090724) and by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (grant number 236611).

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Please cite this article as: A. Björk, Z. Mandalenakis, K.W. Giang, et al., Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital hear..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.01.010