High mortality and morbidity among adults with congenital heart disease and type 2 diabetes

Scandinavian Cardiovascular Journal (ISSN: 1401-7431)

Citation for the published paper:
Dellborg, M. ; Björk, A. ; Pirouzi Fard, M. et al. (2015) "High mortality and morbidity among adults with congenital heart disease and type 2 diabetes". Scandinavian Cardiovascular Journal, vol. 49(6), pp. 344-350.

http://dx.doi.org/10.3109/14017431.2015.1085595

High mortality and morbidity among adults with congenital heart disease and type 2 diabetes

Mikael Dellborg [1*], Anna Björk [1], Mir Nabi Pirouzi Fard [2], Anneli Ambring [2], Peter Eriksson [1], Ann-Marie Svensson [2], Soffia Gudbjörnsdottir [2]

.

[1]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, and adult congenital heart unit, Dept of Medicine, Sahlgrenska University Hospital /Östra, Gothenburg, Sweden.
[2] Centre of Registers in Region Västra Götaland, Gothenburg, Sweden,

* Corrsponding author: phone: +46313434000, fax +4631191416, e-mail: mikael.dellborg@gu.se

Funding; Supported by a grant from the Swedish Heart Lung Foundation (20090724) and by ALF-LUA grants, Sahlgrenska University Hospital

Conflict of Interest: none declared

Presented in abstract form at the American Heart Association yearly sessions November 2012

2758 words

Running title: Congenital heart disease and diabetes

Abstract

Objectives

With improving prognosis the prevalence of adults with congenital heart disease, ACHD, is increasing. Patients with type 2 diabetes mellitus (T2DM) have a shorter life expectancy compared with the general population. We investigated, in a large national diabetes registry, the prevalence of ACHD in combination with T2DM to estimate the associated clinical risk, outcome and patient characteristics.

Design

Data from the Swedish National Diabetes Register (NDR) were linked with the Swedish National Patient Register (NPR) and the Cause of Death Register.

Results

833 ACHD patients were matched with 5 controls each. ACHD patients had significantly lower BMI, higher creatinine and were more sedentary as compared to patients with T2DM but without congenital heart disease.. The overall mortality was 26.2% for ACHD patients as compared to 19.9%, (P<0.001) for the control group and five-year mortality rates were 5.2 vs 3.4%, P=0.014.

Conclusions

Congenital heart disease and secondary risk factors for cardiovascular disease frequently coexist and the development of T2DM also in the ACHD population is not uncommon with an estimated prevalence of between 4 and 8 %. Treatment of conventional cardiovascular risk factors in patients with congenital heart disease could be considered secondary prevention given the relatively high morbidity and high risk for mortality observed in patients with the combination of ACHD and T2DM.

INTRODUCTION

One in 100 of all children are born with a congenital heart defect. Today most of these children live into adulthood and registered data indicate that 90% of them now reach at least 18 years of age (1). The prevalence of adults with congenital heart disease, referred to as adult congenital heart disease (ACHD), has increased consequently and is reported to be 3–4 per 1 000 adults (2). Type 2 diabetes mellitus (T2DM) is associated with an increased risk of microvascular as well as macro-vascular complications, and patients with T2DM have a shorter life expectancy compared with the general population (3). The leading cause of death in patients with T2DM is cardiovascular disease (3). The prevalence of T2DM in the general population is quoted as about 4%, based on registry estimates (4). A Swedish pharmaco-epidemiological report recently published found the prevalence of T2DM to be 4.7%(5). Patients with T2DM are overrepresented in other diseases, including cardiovascular disease, reflecting the negative macro-vascular effects of diabetes.

Obesity and sedentary lifestyle are important risk factors for developing T2DM, and such risk factors may also be prominent in patients with congenital heart diseases (6). The largest study carried out to date reported that only one in five men and women with congenital heart disease had a healthy lifestyle (6). In addition, a relatively small study of predominantly young adults with mostly complex congenital heart disease reported that impaired glucose tolerance was prevalent in this group (7).

To our knowledge, the combined effect of ACHD, including corrective surgery in childhood, and the development of T2DM on mortality and morbidity has not previously been investigated in a large cohort, representing prevalence on a national level.

The aim of the present study was to investigate, in a large national diabetes registry, the prevalence of ACHD in combination with T2DM and to estimate the associated clinical risk, patient characteristics and mortality and morbidity.

METHODS

The Swedish National Diabetes Register (NDR) was established in 1996 as a tool for quality improvement in the care of adult patients with diabetes; it is managed by the Centre of Registers in Region Västra Götaland, Gothenburg, Sweden (8). The register currently includes data from more than 350.000 adult patients with type 1 or type 2 diabetes and >90% Swedish adult patients with diabetes are included in the NDR. Annual reporting to the NDR is based on information collected during patient visits at hospitals and primary health care centres nationwide at least once yearly; it contains data on demographics, duration of diabetes, treatment modalities, cardiovascular risk factors and diabetes complications. To distinguish patients with type 1 diabetes from patients with T2DM in the registry, T2DM was defined in epidemiological terms, namely, treatment with diet only, or treatment with oral hypoglycaemic agents only, or onset age of diabetes $\geq$40 years and treatment with insulin only or in combination with oral agents. All patients in the NDR are above 18 years of age on entry in the register. Data from the NDR were linked with the Swedish National Patient Register (NPR) and the Swedish Cause of Death Register by the unique personal identification number available for all Swedish residents. The NPR includes mandatory information on all principal and secondary discharge diagnoses, classified according to the International Classification of Diseases (ICD). Information on date and cause of death were collected from the Causes of Death Register.

All included patients have agreed by informed consent to be registered in the NDR before inclusion. The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden.

Subjects

For ACHD patients, information was retrieved from the NPR on hospitalisations for congenital heart disease, history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, percutaneous coronary intervention, coronary artery bypass grafting, renal failure and cardiovascular death. This was done by matching the unique personal ID-numbers of all adult patients in the NDR to the NPR.

Congenital heart disease was defined according to ICD 9 codes 745–747 (first 3 number available and ICD 10 codes Q20–28 (first 2 numbers available). Half the patients, 49.8%, consisted of patients with 745, Q20, Q21 i.e. transposition, tetralogy of Fallot, atrial and ventricular septal defects and 23% of patients with codes 747, Q25 i.e mainly patients with coarctation of the aorta .Other ICD 10 codes used were I50 for heart failure, I48 for atrial fibrillation, and I20, I22, I24.8, I24.9 and I25 for ischaemic heart disease.

From NDR and NPR we identified 423 481 adult individuals with diabetes (type 1 or type 2) but without congenital heart disease and 1 860 adults with both diabetes and congenital heart disease, see figure 1. Then from those patients with both diabetes and congenital heart disease we selected 1 330 individuals with T2DM and known year of onset of diabetes. Among T2DM patients without congenital heart disease we selected 323 077 with known year of onset of diabetes. These two groups were then used to select exact matched controls, with five controls per case matched for gender, year of birth, year of onset of diabetes and year of first entry into the register. We excluded patients with unknown duration of diabetes, those with

body mass index (BMI) below 18.5 or above 45 kg/m2, and those with creatinine less than 20 micromoles/l or more than 800 micromoles/l. Thus, a final study population of 833 cases, made up of individuals with T2DM and congenital heart disease, was compared to 4 165 controls with T2DM but without congenital heart disease. The follow-up period was until death or 31 June 2012.

Statistical analysis

Normally distributed data are presented as mean (standard deviation) and non-parametric data are presented as median (interquartile range, IQR). Tests for trend in proportions were conducted using nonparametric 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).

RESULTS

The number of T2DM in Swedish ACHD patients, as determined by the present registries, was 1330. The exact number of adult congenital heart patients in Sweden is not known. Therefore we estimated the number of ACHD-patients in Sweden using the nationwide SWEDCON quality registry that includes 17436 adult patients with congenital heart disease (9). Using this number, we estimated the prevalence of diabetes type 2 to be 7.6% among

ACHD patients (i.e. 1330/17436). If we instead used a population based estimate from Quebec (2), applying the Canadian prevalence of 0.4% also on the adult population in Sweden, the estimate indicates that there are 32.000 adult patients with congenital heart disease. This prevalence of T2DM could then be calculated to be 4.2% among Swedish ACHD patients. The characteristics of cases and controls and the data at the last registration in the NDR register are given in table 1. ACHD patients had a slightly shorter, nominally significant duration of diabetes than controls (8±6 years vs 9±6 years, *P*=0.047) and had significantly lower BMI, higher creatinine and a trend (*P*=0.059) towards somewhat lower systolic blood pressure. Lifestyle factors differed across the groups: ACHD-patients reported being significantly more sedentary and 39.5% reported engaging in physical activity never or less than once a week compared to 33.3% of the control group, see table 2. However, ACHD patients were less often smokers (10.7% vs 14.1%, *P*=0.011). Medical treatment of diabetes, hypertension and lipids were similar in the two groups (table 2). The only significant difference was in use of aspirin which was give to 45.9% of patients with T2DM , significantly more than the 41.8% of patients with T2DM and ACHD that were given aspirin (p=0.038).. As T2DM is frequently diagnosed in connection with hospitalisation for other diseases, we examined the incidence of other cardiovascular diseases in the year *before* diabetes diagnosis. From table 3 it is evident that congestive heart failure and atrial fibrillation are significantly more prominent during the year before onset of T2DM in ACHD patients compared to controls. Similar findings are also seen when extending the observation period back to 1987 (table 4). In addition, stroke is significantly more prevalent among ACHD patients with T2DM as compared to patients with only T2DM.

From onset of diabetes till end of follow-up on 30 june, 2012, a total of 218 patients with T2DM and diabetes died, as compared to 828 patients in the control group, for a mortality of 26.2% for ACHD patients as compared to 19.9%, (*P*<0.001) for the control group,The log

rank survival estimate differed significantly between groups ($P<0.0001$) with higher mortality for ACHD patients (figure 2). This was evident already at five years after onset of diabetes; five-year mortality rates were 5.2 vs 3.4%, $P=0.014$, ten year mortality was 13.7% vs 9.7% ($p<0.001$).

DISCUSSION

Advances in diagnostic and surgical techniques in the last decade have significantly increased the life expectancy of patients with congenital heart disease, which has resulted in a large ACHD population (1,2). In a similar time frame the prevalence of T2DM has increased (10). Our study identified a large number of patients with T2DM and congenital heart disease, all adults. The mean age of the patients with ACHD in the current study was 70 years which reflects a large proportion of patients with more benign lesions such as atrial or ventricular septal defects. Almost a quarter of the patients was made up of patients with coarctation of the aortae, a macrovascular malformation that has been reported to be associated with atherosclerotic disease (11) As the ACHD-population ages, it is as likely to develop secondary cardiovascular and metabolic disease as the general population (2). To study the impact of two diagnoses with a relatively low prevalence in a population comparatively large studies are needed and large number of patients are also needed to assess clinical characteristics, and to estimate the outcome in patients with the combined cardiovascular stress of congenital heart disease and T2DM. The exact prevalence of congenital heart disease in adults in Sweden is not known but based on national registries (9) and international, population based databases (2), the prevalence of T2DM in ACHD patients in Sweden is estimated to be between 4,2 and 7,6%. This is comparable to findings from pharmaco-epidemiological studies in Sweden, where the prevalence of T2DM was 4.7% (5) Our data thus indicate at least a similar or higher prevalence of T2DM among ACHD-patients. The

increase in prevalence of T2DM observed in the general population may thus be reflected also among ACHD patients. The prevalence of lifestyle risk factors in our study suggests that a sedentary lifestyle may be an especially prominent problem in ACHD patients is in line with findings from other studies (12). A large observational study from the NDR of patients with T2DM showed considerably increased risks for cardiovascular disease and mortality with low physical activity (13). Obesity has a negative impact on early postoperative recovery among ACHD -patients undergoing repeat surgery, although no direct influence on postoperative mortality has been shown (14). This is true also for other patient groups but in general ACHD-patients are believed to be at increased risk for cardiac surgery, as compared to patients without congenital heart disease. Conventional risk factors will also apply to and affect ACHD patients, although the proportion has so far been relatively low, presumably due to the low mean age of ACHD patients (15).

The current study indicates a comparatively high mortality for the ACHD patients with diabetes compared to non-ACHD patients with diabetes and the five-year mortality rate of 5.2 vs 3.4% represents a statistically significant difference. The current study did not include a control population with congenital heart disease but without diabetes, which makes it hard to draw conclusions regarding the impact of diabetes on mortality in patients with congenital heart disease. It is possible that the excess mortality detected is related mainly to the congenital heart disease itself rather than the influence of diabetes in combination with congenital heart disease. On the other hand, it would be surprising and counterintuitive, if adult patients with congenital heart disease were not adversely affected by the development of T2DM. It is worth noting that while arrhythmias and heart-failure are more common among patients with the combination of ACHD and T2DM, atherosclerotic manifestations were equally common among cases and controls (table 3). T2DM is associated with an increased risk of developing atherosclerotic disease, regardless of the presence of a congenital

malformation or not. The ACHD-cardiologist needs to be aware of the existence, and importance, of T2DM among elderly ACHD-patients.

Conventional risk factors for the development of coronary artery disease are associated with the occurrence of additional coronary artery disease in ACHD-patients, just as they are in the general population (16) and it has been suggested that coronary angiography should be routinely performed in ACHD-patients referred for cardiac surgery once they are above 40 years of age (17). Indeed, one may speculate that type 2 diabetes and its associated cardiac and vascular complications can be expected to have an even larger impact in the ACHD population, especially given the expected need for repeat surgical or endovascular corrective interventions.

If applying a risk-based assessment and indications for treatment, as for instance is done in latter day lipid lowering treatment guidelines, then lipid-lowering treatment, treatment with aspirin, and blood pressure control in patients with congenital heart disease may all be considered equivalent to secondary prevention, as treatment focusing on a specific group of patients with increased risk. We found that patients with congenital heart disease in addition to their diabetes were as likely to receive antihypertensive and lipid-lowering drugs as those with T2DM only but, somewhat unexpectedly, were less frequently given aspirin. One possible explanation may be more frequent use of warfarin for specific indications, namely, atrial arrhythmias and mechanical heart valves. While 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 (18, 19). Our current data showing less aspirin treatment for these patients, in combination with their substantially higher mortality than the control group with T2DM only, makes a case for treatment with aspirin and lipid-lowering treatment as secondary preventive measures in patients with T2DM and congenital heart disease. At the same time, one must be aware that the evidence in favour of treating secondary

risk factors in a more aggressive manner in patients with co-existing congenital heart disease is an extrapolation from previous clinical trials including few if any patients with congenital heart conditions (20, 21). But lack of evidence must not be equated with lack of benefit. It is highly unlikely that large, randomised studies of, for example, cholesterol-lowering treatment in ACHD patients will ever be conducted, and they might even be considered unethical. Our data further strengthen the need for lifestyle advice for ACHD patients, further supporting the importance for adults with congenital heart disease to attend specialised ACHD units (22). Our data suggest that early identification of an unhealthy lifestyle is important for GUCH-patients and routine screening with measurements of HbA1c, lipid levels and blood pressure may be considered appropriate for ACHD patients with increasing age.

Conclusion

Congenital heart disease and secondary risk factors for cardiovascular disease frequently coexist and the development of T2DM in the ACHD population is not uncommon with a calculated prevalence of between 4 and 8 %. Our data suggest that the treatment and adjustment of conventional cardiovascular risk factors in patients with congenital heart disease may be important and could be considered risk-level based secondary prevention considering the higher risk for mortality observed in patients with the combination of ACHD and T2DM.

Limitations

The current study is based on registry data, which is limited in the amount and precision of data recorded, and the number of patients in the study is comparatively modest. We lack more detailed information as to the impact of prognostic factors associated with congenital heart

disease, such as the specific subtype of congenital heart disease, exercise capacity, number and complexity of previous surgeries, and general co-morbidities and we also lack a comparative group of patients with ACHD but without diabetes. Also, the comorbidities normally associated with ACHD are not available in the data used for the current study.

Acknowledgements

We thank all the regional NDR coordinators, contributing nurses, physicians and patients.

References

1. 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: 2264-2272
2. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M.. Congenital heart disease in the general population: changing prevalence and age distribution. Lifetime Prevalence of Congenital Heart Disease in the General Population From 2000 to 2010 Circulation. 2014;130:749-56.
3. 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;21:539-45
4. https://www.ndr.nu/pdf/Annual_Report_NDR_2013.pdf
5. Jansson SP, Fall K, Brus O, Magnuson A, Wändell P, Östgren CJ, Rolandsson O. Prevalence and incidence of diabetes mellitus: a nationwide population-based pharmaco-epidemiological study in Sweden. Diabet Med. 2015, doi: 10.1111/dme.12716.
6. 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;13:612-16
7. 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;158:30-39
8. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B; Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care. 2003;4:1270-6.
9. http://www.ucr.uu.se/swedcon/index.php/arsrapporter (May 22, 2015)
10. 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;94:311–21
11. 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;80:840-5.

12. 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;109:1657-63
13. Zethelius B, Gudbjörnsdottir S, Eliasson B, Eeg-Olofsson K, Cederholm J. Level of physical activity associated with risk of cardiovascular disease and mortality in patients with type-2 diabetes: report from the Swedish National Diabetes Register. Eur J Prev Cardiol 2014;21:244-51
14. Zaidi A, Bauer J, Michalsky M, 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;6:241-246
15. Yalonetsky S, Horlick E, Osten M, Benson L, Oechslin E, Silversides C. Clinical characteristics of coronary artery disease in adults with congenital heart defects. Int J Cardiol 2013;164:217-220
16. Roifman I, Therrien J, Ionescu-Ittu R, Pilote L, Guo L, Kotowycz M, et al. Coarctation of the aorta and coronary artery disease: fact or fiction ? Circulation 2012;126:16-21
17. Giannakoulas G, Dimipoulos 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;103:1445-1450
18. 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
19. Schnell O, Erbach M, Hummel M. Primary and secondary prevention of cardiovascular disease in diabetes with aspirin. Diab Vasc Dis Res. 2012;9:245-55.
20. Wu HY, Huang JW, Lin HJ, Liao WC, Peng YS, Hung KY, et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ. 2013;347:f6008.
21. Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol. 2013;20:641-57.

22. Mylotte D, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J, et al. Specialized adult congential heart disease care: the impact of policy on mortality. Circulation. 2014;129:1804-12

Tables

Table 1. Characteristics of ACHD patients with T2DM and patients with T2DM only (continuous variables).

	ACHD+T2DM (n=833)	**T2DM (n=4165)**	***P-value***
Last registration †	median (interquartile range) (n)	median (interquartile range) (n)	
Age in years	70 (62-78) (833)	70 (62-78) (4165)	0.277
Diabetes duration, years	7(4-11,5) (833)	8 (4-12) (4165)	0.047
Waist measurement, cm	102 (94-112) (526)	102 (95-112) (2858)	0.580
BMI, kg/m^2	28.4 (25.2-31.9) (788)	28.8 (25.9-32.4) (3982)	0.009
Systolic blood pressure, mm Hg	133 (125-145) (823)	135 (125-145) (4107)	0.059
HbA1c (IFCC), mmol/mol	51 (45-61) (823)	52 (52-65) (4165)	0.313
Creatinine,μmol/l	78 (66-97) (767)	77 (66-93) (3885)	0.038

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
ACHD+T2DM: adult congenital heart disease and T2DM, Control: Patients with T2DM only, BMI: body mass index HbA1c: glycosylated haemoglobin A1c
Data presented as median (IQR) and n (%)

Table 2. Characteristics of ACHD patients with T2DM and patients with T2DM only at last visit.

	ACHD+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), 0.011
Microalbuminuria	28 (717)	25 (3677)	1.49 (0.96,1.37), 0.129
Antihypertensive agents	82 (824)	79 (4110)	1.18 (0.97,1.43), 0.093
Lipid-lowering agents	58 (806)	59 (4067)	0.98 (0.84,1.14), 0.771
Acetylsalicylic acid, aspirin	42 (763)	46 (3935)	0.85 (0.72,0.99), 0.038
Diet only	23 (833)	23 (4162)	1.01 (0.84,1.20), 0.960
OHA*** only	44 (833)	44 (4162)	0.97 (0.84,1.13), 0.728
OHA and insulin	17 (833)	18 (4162)	0.93 (0.76,1.13), 0.440
Insulin only	16 (833)	15 (4162)	1.13 (0.92,1.38), 0.239
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), 0.087
Regular ≥3-5 times/week	42 (678)	45 (3636)	0.87 (0.74,1.03), 0.107

^ Days at hospital at least 3 days before debut year
*Odds ratio **Confidence interval ***Oral hypoglycaemic agents
ACHD+T2DM: adult congenital heart disease and T2DM, control: patients with T2DM only .

Table 3. Incidence of cardiovascular diseases one year before year of diabetes onset

Disease	**ACHD+T2DM**	**T2DM**	***P*-value**
	% (n)	**% (n)**	
Ischaemic heart disease	1.9 (16)	1.8 (76)	0.851
Atrial fibrillation	3.2 (27)	0.77 (32)	<.0001
Heart Failure	2.4 (20)	0.91 (38)	<.0001
Stroke	0.60 (5)	0.77 (32)	0.606
PCI	0.36 (6)	0.67 (28)	0.295
CABG	0.48 (4)	0.34 (14)	0.524*
Renal failure	0.24 (2)	0.07 (3)	0.196*
Any CVD	2.9 (24)	2.9 (121)	0.970

*Fisher exact test

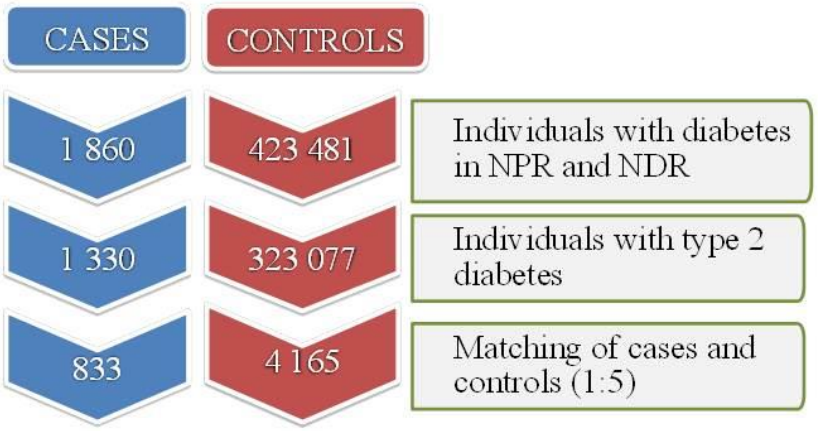
ACHD+T2DM: adult congenital heart disease and T2DM, Control: patients with T2DM only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CVD: cardiovascular disease.

Table 4. Cumulative incidence of cardiovascular diseases from 1987 to year of diabetes diagnosis.

Disease	ACHD+T2DM % (n)	T2DM % (n)	*P*-value
Ischaemic heart disease	12.7 (106)	11.0 (460)	0.162
Atrial fibrillation	10.9 (91)	3.2 (131)	<.0001
Heart failure	10.6 (88)	3.8 (157)	<.0001
Stroke	13.3 (111)	4.0 (165)	<.0001
PCI	2.5 (22)	3.2 (131)	0.441
CABG	3.7 (31)	3.2 (132)	0.413
Renal failure	0.84 (7)	0.46 (19)	0.159
Any CVD	24 (200)	15 (623)	<.0001

ACHD+T2DM: adult congenital heart disease and T2DM, Control: patients with T2DM only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting. CVD: cardiovascular disease.

Figure 1

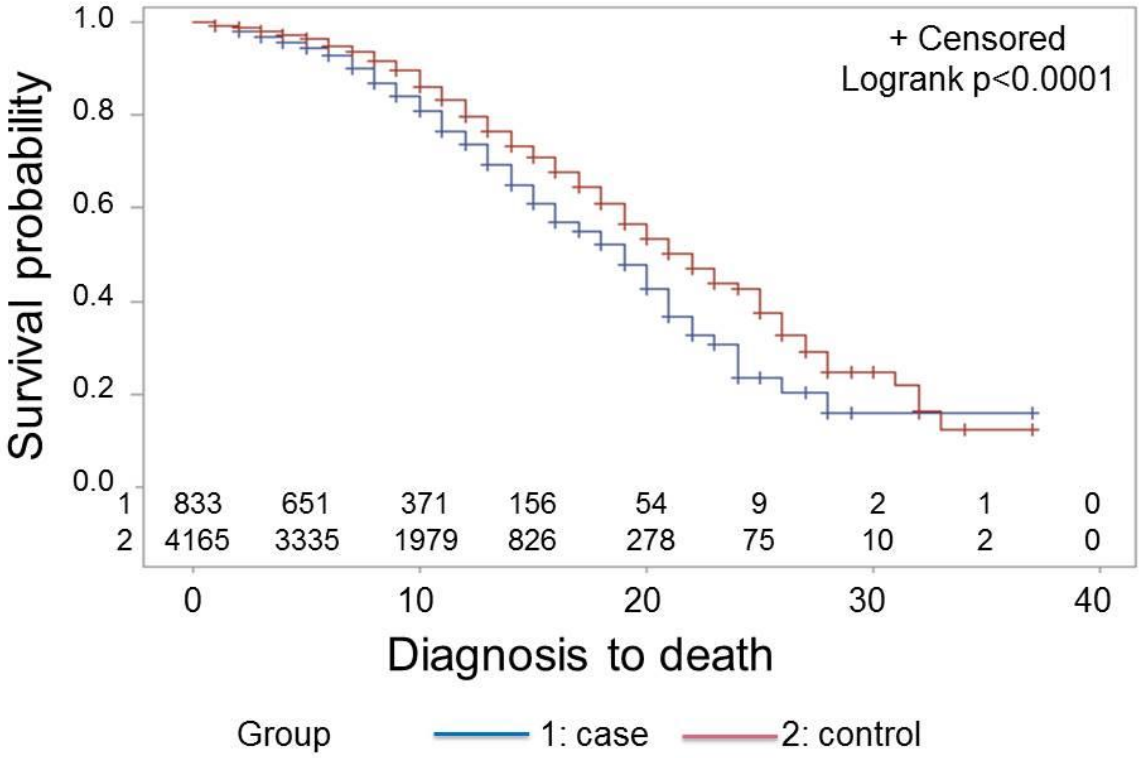


Study design.

There were 425375 individuals in the National Patient Register (NPR) and 541038 adults in the National Diabetes Registry (NDR). A case-control study was performed and, by merging NPR with NDR, 423481 diabetes diagnoses could be found in this 83-year period. A total of 323077 were unique individuals with type 2 diabetes, sorted by national personal identity number and given individual patient IDs. 1860 unique patients with diabetes (type 1 or type 2) and congenital heart defects could be identified (cases) and 1330 with congenital heart defects and type 2 diabetes. After exclusions and matching, a total of 833 cases were included in this study, matched to 4165 controls.

Cases: adult patients with congenital heart disease and type 2 diabetes mellitus. Controls: patients with type 2 diabetes mellitus only.

Figure 2



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