

SUPPLEMENTAL MATERIAL

Table S1. International Classification of Diseases diagnosis codes according to lesion group .

Lesion group	CHD diagnoses included in the group	ICD-10	ICD-9	ICD-8
1. Conotruncal defects	Common truncus	Q200	745A	746.0
	Aortopulmonary septal defect	Q214	745A	746.0
	Transposition of the great vessels	Q201– 203	745B	746.1
	Tetralogy of Fallot	Q213	745C	746.2
2. Severe non-conotruncal defects	Endocardial cushion defect	Q212	745G	746.47
	Common ventricle	Q204	745D	746.37
	Hypoplastic left heart syndrome	Q234	746H	746.74
3. Coarctation of the aorta	Coarctation of the aorta	Q251	747B	747.19

4. Ventricular septal defect	Ventricular septal defect	Q210	745E	746.39
		Q218	754W	746.89
5. Atrial septal defect	Atrial septal defect	Q211	745F	745.42
				746.43
				746.46
6. Other heart and circulatory system anomalies	All congenital heart disease diagnoses not included in the five categories above			

CHD, congenital heart disease; ICD, International Classification of Diseases.

Table S2. International Classification of Diseases diagnosis codes for comorbidities and cardiovascular death used in the study.

Diagnosis	ICD-8	ICD-9	ICD-10
Hypertension	400-404	401-405	I10-I15
Diabetes	250	250	E10-E14
Hyperlipidemia	272-272,01	272A, 272E	E780, E782, E784, E785
Atrial fibrillation	427.92	427D	I48
Ischemic stroke	433, 434	434, 436	I63, I64
Myocardial infarction	410	410	I21
Cardiovascular death	410, 433, 434	410, 434, 436	I21, I63, I64

ICD=International Statistical Classification of Diseases

Table S3. Baseline characteristics of CHD patients with DS by birth period

	1970–1989 (N=956)	1990–2017 (N=2329)	P-value
Female	500 (52.3%)	1091 (46.8%)	
Year of birth, SD, Median (IQR)*	1980.3±5.7 1980 (1975;1985)	2003.7±7.8 2004 (1997;2010)	<0.001
Follow-up (years), Median (IQR)*	25.7±16.2 31.6 (4.0;38.5)	12.7±8.0 12.0 (5.8;19.5)	<0001
Lesion complexity			<0.001
Complex CHD	517 (54.1%)	921 (39.5%)	
-Univentricular heart	81 (8.5%)	74 (3.2%)	
Non-complex CHD	439 (45.9%)	1408 (60.5%)	

CHD, congenital heart disease; DS, Down syndrome; SD, standard deviation; IQR, interquartile range. * Continuous variable.

P<0.05 was considered statistically significant.

Table S4. Distribution of birth year for patients with CHD and DS and matched controls.

	CHD and DS (n=3285)	Controls without DS or CHD (n=26128)
Birth year, (%)		
1970	36 (1.1)	259 (1.0)
1971	28 (0.9)	197 (0.8)
1972	40 (1.2)	297 (1.1)
1973	44 (1.3)	327 (1.3)
1974	50 (1.5)	357 (1.4)
1975	45 (1.4)	292 (1.1)
1976	37 (1.1)	245 (0.9)
1977	48 (1.5)	323 (1.2)

1978	42 (1.3)	256 (1.0)
1979	49 (1.5)	304 (1.2)
1980	61 (1.9)	406 (1.6)
1981	45 (1.4)	301 (1.2)
1982	43 (1.3)	265 (1.0)
1983	48 (1.5)	311 (1.2)
1984	50 (1.5)	319 (1.2)
1985	54 (1.6)	351 (1.3)
1986	55 (1.7)	367 (1.4)
1987	60 (1.8)	394 (1.5)
1988	62 (1.9)	440 (1.7)
1989	59 (1.8)	449 (1.7)

1990	72 (2.2)	532 (2.0)
1991	81 (2.5)	625 (2.4)
1992	85 (2.6)	666 (2.5)
1993	84 (2.6)	655 (2.5)
1994	89 (2.7)	709 (2.7)
1995	73 (2.2)	564 (2.2)
1996	71 (2.2)	562 (2.2)
1997	54 (1.6)	420 (1.6)
1998	69 (2.1)	539 (2.1)
1999	63 (1.9)	505 (1.9)
2000	70 (2.1)	548 (2.1)
2001	90 (2.7)	728 (2.8)

2002	89 (2.7)	744 (2.8)
2003	112 (3.4)	952 (3.6)
2004	86 (2.6)	719 (2.8)
2005	99 (3.0)	829 (3.2)
2006	116 (3.5)	995 (3.8)
2007	80 (2.4)	682 (2.6)
2008	105 (3.2)	922 (3.5)
2009	94 (2.9)	803 (3.1)
2010	87 (2.6)	787 (3.0)
2011	101 (3.1)	894 (3.4)
2012	90 (2.7)	817 (3.1)
2013	76 (2.3)	693 (2.7)

2014	88 (2.7)	793 (3.0)
2015	74 (2.3)	708 (2.7)
2016	67 (2.0)	641 (2.5)
2017	64 (1.9)	636 (2.4)
CHD, congenital heart disease; DS, Down syndrome;		

Table S5. Risk of mortality in patients with CHD and DS compared with matched controls by age group and birth period.

Age group	HR for mortality (95% CI)		
	Overall	1970–1989	1990–2017
With CHD patients without DS as a reference			
0–0.9 years	1.35 (1.19–1.53)	1.11 (0.93–1.32)	1.36 (1.13–1.65)
1–9 years	4.70 (4.01–5.50)	4.67 (3.92–5.77)	3.70 (2.81–4.88)
10–17 years	2.71 (1.89–3.88)	3.19 (2.07–4.93)	1.98 (1.03–3.81)
18+ years	3.28 (2.61–4.13)	3.70 (2.92–4.68)	0.82 (0.26–2.60)
With controls without CHD or DS as a reference			
0–0.9 years	26.91 (20.81–34.79)	46.76 (29.53–74.04)	17.69 (12.82–24.42)
1–9 years	55.64 (37.86–81.77)	70.03 (41.67–117.68)	37.33 (20.85–66.86)

10–17 years	44.19 (19.59–99.69)	56.86 (19.73–163.88)	29.43 (8.10–106.95)
18+ years	10.43 (7.72–14.10)	11.62 (8.49–15.89)	2.78 (0.77–10.11)

CHD, congenital heart disease; DS, Down syndrome; HR, hazard ratio; CI, confidence interval.

Table S6. Risk of mortality in patients with CHD and DS compared with matched CHD patients without DS and compared with matched controls, according to gender, lesion complexity and divided by age groups and birth periods.

	HR for mortality (95% CI)	
With CHD patients without DS as reference		
	1970-1989	1990-2017
Male		
All	2.04 (1.75–2.37)	1.41 (1.13–1.76)
0–0.9 years	1.11 (0.87–1.41)	1.20 (0.92–1.58)
1–9 years	4.62 (3.50–6.09)	2.69 (1.74–4.16)
10-17 years	4.14 (2.42–7.09)	1.10 (0.34–3.52)
18+ years	3.09 (2.20–4.34)	1.21 (0.38–3.91)
Female		
All	2.17 (1.86–2.53)	2.10 (1.71–2.58)
0–0.9 years	1.31 (0.88–1.45)	1.56 (1.19–2.03)
1–9 years	4.92 (3.75–6.46)	4.86 (3.38–6.97)

10-17 years	2.23 (1.07–4.67)	3.03 (1.36–6.74)
18+ years	4.61 (3.31–6.43)	N/A
Lesion complexity		
Complex		
All	0.99 (0.87–1.13)	0.57 (0.47–0.69)
0–0.9 years	0.52 (0.42–0.64)	0.42 (0.33–0.54)
1–9 years	1.81 (1.44–2.28)	1.37 (0.95–1.98)
10-17 years	1.44 (0.87–2.40)	1.09 (0.50–2.39)
18+ years	2.46 (1.80–3.38)	N/A
Non-complex		
All	1.85 (1.52–2.26)	1.68 (1.33–2.13)
0–0.9 years	1.14 (0.84–1.55)	1.43 (1.06–1.92)
1–9 years	4.42 (3.03–6.46)	3.11 (1.99–4.87)
10-17 years	2.11 (0.85–5.23)	0.95 (0.23–3.88)
18+ years	2.60 (1.75–3.89)	1.80 (0.56–5.79)
Age groups		

0-0.9 years	1.11 (0.93-1.32)	1.36 (1.13-1.65)
1-9 years	4.67 (3.92-5.77)	3.70 (2.81-4.88)
10-17 years	3.19 (2.07-4.93)	1.98 (1.03-3.81)
18+ years	3.70 (2.92-4.68)	0.82 (0.26-2.60)
With controls without CHD or DS as reference		
	1970-1989	1990-2017
Male		
All	25.51 (19.18-33.92)	15.49 (10.87-22.06)
0-0.9 years	37.49 (20.71-67.86)	14.74 (9.59-22.66)
1-9 years	89.74 (38.84-207.35)	40.82 (15.52-107.38))
10-17 years	38.24 (12.78-114.37)	13.08 (2.19-78.29)
18+ years	9.97 (6.41-15.51)	3.34 (0.89-12.61)
Female		
All	31.87 (23.42-43.36)	25.52 (17.29-37.66)
0-0.9 years	61.74 (29.67-128.45)	22.10 (13.51-36.14)
1-9 years	58.15 (29.94-112.94)	35.42 (17.06-73.53)

10-17 years	N/A	62.84 (7.74–510.99)
18+ years	13.78 (8.80–21.57)	N/A
Lesion complexity		
Complex		
All	36.06 (27.81–46.76)	25.53 (17.74–36.75)
0–0.9 years	68.70 (35.83–131.74)	19.85 (12.84–30.70)
1–9 years	77.72 (42.70–141.47)	57.52 (24.32–136.07)
10-17 years	52.08 (17.72–153.10)	N/A
18+ years	15.27 (10.35–22.51)	N/A
Non-complex		
All	19.11 (13.39–27.28)	14.45 (9.90–21.08)
0–0.9 years	27.08 (13.94–52.61)	15.26 (9.43–24.68)
1–9 years	60.49 (21.35–171.36)	22.87 (10.13–51.63)
10-17 years	N/A	5.63 (0.94–33.68)
18+ years	8.15 (4.78–13.90)	4.25 (1.06–16.99)
Age groups		

0–0.9 years	46.76 (29.53–74.04)	17.69 (12.82–24.42)
1–9 years	70.03 (41.67–117.68)	37.33 (20.85–66.86)
10–17 years	56.86 (19.73–163.88)	29.43 (8.10–106.95)
18+ years	11.62 (8.49–15.89)	2.78 (0.77–10.11)

CHD defines as congenital heart disease; DS defines as Down syndrome; HR defines as hazard ratio;

CI defines as confidence interval, N/A= Indicates to few events to estimate HR.

Figure S1. Flowchart of identification of CHD patients with DS. CHD, congenital heart disease; DS, Down syndrome.

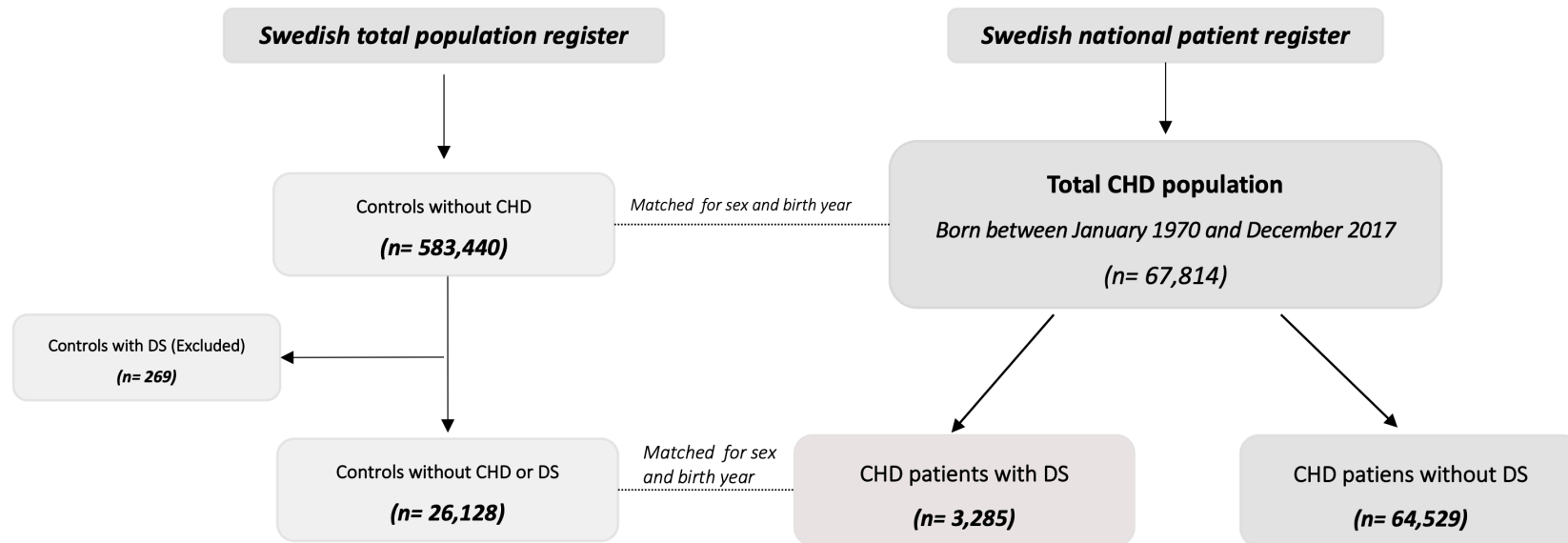


Figure S2. Kaplan–Meier survival curves of patients with CHD and DS, matched controls, and CHD patients without DS by complexity of the lesion. CHD, congenital heart disease; DS, Down syndrome.

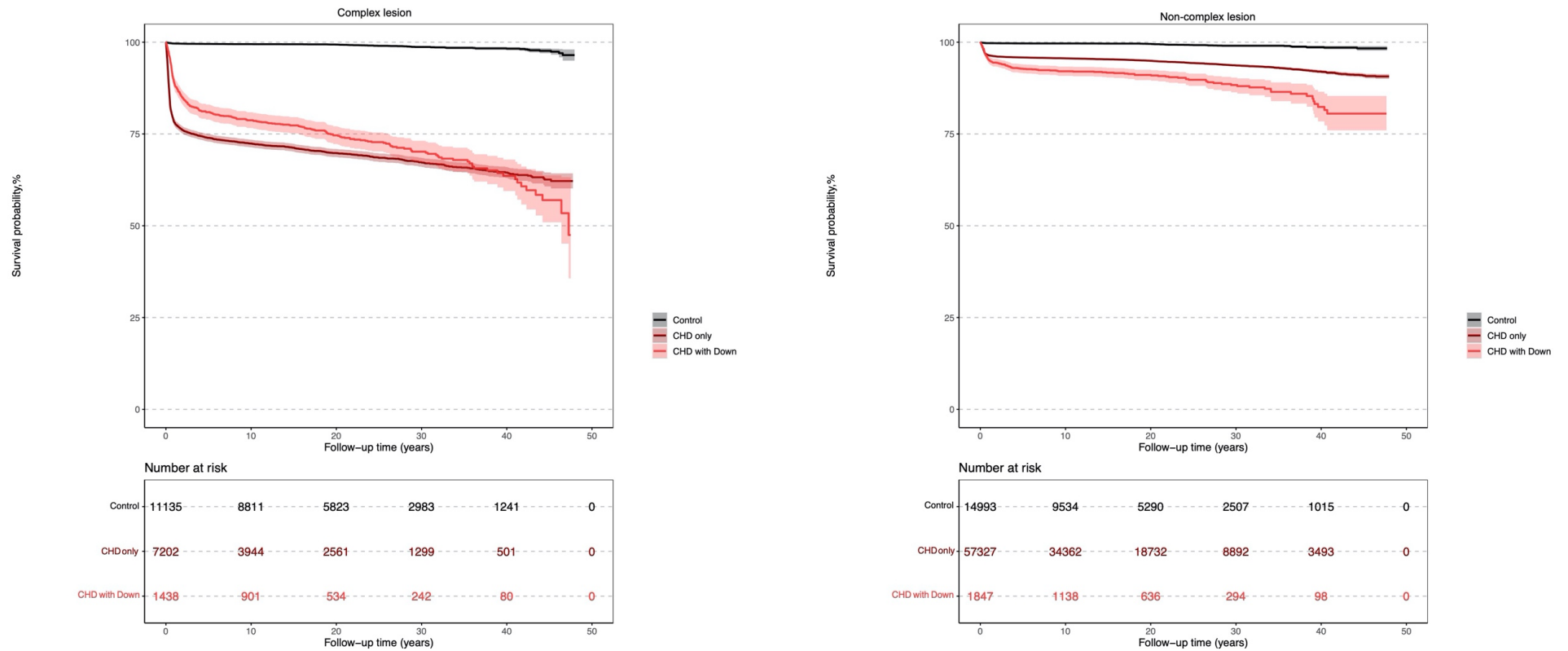


Figure S3. Kaplan–Meier survival curves of patients with CHD and DS, matched controls, and CHD patients without DS by sex. CHD, congenital heart disease; DS, Down syndrome.

