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ORIGINAL ARTICLE

Familial risk of dilated and hypertrophic cardiomyopathy: a national family study in Sweden

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Abstract

Aims This study aims to determine the familial incidence of dilated (DCM) and hypertrophic cardiomyopathy (HCM) in first-degree, second-degree, and third-degree relatives of affected individuals.

Methods and results In this population-based multigenerational cohort study, full-siblings, half-siblings, and cousin pairs born to Swedish parents between 1932 and 2015 were included, and register-based DCM and HCM diagnoses among relatives were ascertained. Adjusted odds ratios (ORs) for DCM and HCM were calculated for relatives of individuals with DCM and HCM compared with relatives of individuals without DCM and HCM for reference. Total study population included 6 334 979 subjects and consisted of 5 577 449 full-siblings, 1 321 414 half-siblings, and 3 952 137 cousins. Overall, 10 272 (0.16%) unique individuals were diagnosed with DCM and 3769 (0.06%) with HCM. Of these, 7716 (75.12%) and 2375 (63.01%) were males, respectively. Familial risk ORs for DCM were 5.35 [95% confidence intervals (CI): 4.85–5.90] for full-siblings, 2.68 (95% CI:1.86–3.87) for half-siblings, and 1.72 (95% CI:1.12–2.64) for cousins of affected individuals. The ORs for HCM were 42.44 (95% CI:37.66–47.82) for full-siblings, 32.70 (95% CI:21.32–50.15) for half-siblings, and 36.96 (95% CI:29.50–46.31) for cousins of affected individuals. In sex-stratified analysis, relatives of affected females were found more likely to be affected than were relatives of affected males, with stronger aggregation observed for HCM.

Conclusions Familial risk of HCM and DCM is high and associated with genetic resemblance, with strongest aggregations observed in relatives of affected females with HCM, whereas this association was distinctly attenuated for DCM. The finding of a Carter effect, more pronounced in HCM, suggests a multifactorial threshold model of inheritance.

Keywords Epidemiology; Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Familial risk; Heart muscle disease; Inherited cardiomyopathies

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Introduction

Cardiomyopathies are a heterogeneous group of inherited (genetic/familial) and acquired heart muscle disorders unexplained solely by coronary artery disease or abnormal loading conditions.[1,2] Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are the most common cardiomyopathies[3–5] typically progressing to heart failure and causing arrhythmic events. The estimated prevalence of DCM ranges from 1:250 to 1:500 in the general population,[3,4,6,7] whereas the prevalence of HCM has been estimated to range from 1:200 to 1:500 for asymptomatic cases, and <1:3000 for symptomatic cases.[3,7–9] A diagnosis of DCM is made on the basis of established criteria that define left ventricular (LV) dilatation and systolic function impairment,[3,4] with expression of disease usually occurring during adulthood and with a twofold greater prevalence in men.[10] HCM is characterized by LV hypertrophy that is

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accompanied by enhanced cardiac contractility and impaired relaxation, in the absence of other non-sarcomeric cardiac, systemic, or metabolic phenocopies explaining the magnitude of increased wall thickness.[8]

DCM and HCM have been described to be inherited in a proportion of families with mainly an autosomal dominant pattern.[3–5] Since the discovery of disease causing variants in the *MYH7* gene in HCM[1,11,12] and in the *ACTC1* gene in DCM,[13] more than 1000 rare pathogenic variants have been reported in HCM and DCM families and in individual patients.[14,15] Pathogenic or likely pathogenic variants in sarcomere protein genes account for 30–60% of HCM cases, a range that reflects diagnostic criteria[16] and contemporary approaches to variant classification.[17] Recent genome-wide association studies have also shown that DCM and HCM have strong polygenic contributions.[18–20] Thus, not only cardinal genes but also polygenes are of importance for the development of DCM and HCM, particularly for sarcomere-negative phenotypes.[15]

Familial risks for DCM and HCM in a large population-based family cohort study have not yet been determined. Accordingly, we aimed to investigate the familial incidence of DCM and HCM by examining full-siblings, half-siblings, and cousins, in a large nationwide Swedish family database linked to national patient registry.[21,22]

Methods

Study population

All data were provided by Statistics Sweden and the National Board of Health and Welfare for research purposes. Data were coded according to European Union law. The Regional Ethical Review Board in Lund, Sweden, approved this cohort study and waived informed consent as a requirement. This study followed the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' reporting guideline. We used the following Swedish national registers for data extraction[21–25]: the Swedish Multi-Generation Register, which contains data on familial relationships and index persons born in 1932 and later and registered in Sweden 1961 and later; the National Patient Register, which includes all hospital discharge diagnoses from 1964 to 2015 and nationwide coverage from 1987 and hospital outpatient diagnoses from 2001 to 2015; the national statistical register, which contains data on death date, if applicable, name change, marital status, family relationships, education, and migration (the register has high coverage for nearly 100% of birth and death dates, 95% of immigration events, and 91% for emigration events); and the Swedish Cause of Death Register, which provides date and cause of death from 1961 to 2015. The databases were linked together according to previously applied methods.[26,27]

In the Swedish Multi-Generation National Swedish Register,[21] we identified all pairs of full-siblings, half-siblings, and cousins born in Sweden by Swedish-born parents. Thus, both biological parents were obligatorily known. Relative pairs with members who died or emigrated before 1997 or emigrated before the age of 17 years were excluded. Three different data sets were created: full-siblings, half-siblings, and cousins. Twins were included in the full-sibling group, and no information regarding zygosity were available. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) I42 was used to identify cardiomyopathy. We identified individuals with a diagnosis of cardiomyopathy (ICD-10 code I42) registered between 1997 and 2015 from the National Patient Register. DCM was identified by I42.0 and HCM by I42.1 and I42.2 codes. Restrictive cardiomyopathy was identified by I42.5, but two few individuals with this condition were identified for study of familial risks (*Table S1*). No specific diagnostic codes for arrhythmogenic cardiomyopathy and amyloid cardiomyopathy are available, so these possibly inherited cardiomyopathies could not be studied. The validity of DCM and HCM in the Swedish register has been previously reported to be 85.5% and 87.5%, respectively.[28] However, a study by Magnusson *et al*. found a validity of only 68.2% for HCM.[29] Sensitivity analysis was therefore performed with exclusion of potential aetiological differential diagnosis (*Tables S2* and *S3*).

In the database, all relative pairs were double-entered (i.e. all full-sibling pairs, all half-sibling pairs, and all cousin pairs, as previously described).[26,27] We allowed the same person to be included in more than one family relationship.

Statistical analysis

Incidence rates were defined as the number of events divided by the person-time at risk. The familial incidence ratio between two incidence densities (rate in the exposed population divided by rate in those unexposed) gave the incidence rate ratio (IRR). DCM and HCM cardiomyopathy-free survival curves were constructed according to the Kaplan–Meier method to compare individuals with and without relative history of respective cardiomyopathy. For comparison of two curves, the log-rank test, resulting in a test statistic with a χ^2 distribution and 1 *df*, was used. The adjusted familial associations between full-siblings', half siblings', and cousins' cardiomyopathy (DCM and HCM) events were investigated with logistic regression. Results are reported as familial odds ratios (ORs) and 95% confidence intervals (CIs). Models were adjusted for year of birth, sex, level of education, coronary heart disease (I20–I25), hypertension I10, atrial fibrillation (I48), diabetes (E10–E14), aortic stenosis (I060, I350), chronic obstructive pulmonary disease (J40–J47), and cancer (C00–C97). Familial ORs for cardiomyopathy

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(DCM or HCM) were calculated for relatives of individuals who had a diagnosis of cardiomyopathy compared with relatives of individuals unaffected by cardiomyopathy as the reference group. A sensitivity analysis was performed by excluding all individuals with potential differential diagnosis for DCM and HCM, respectively. Another sensitivity analysis was performed based on cousins' years of birth that included full-siblings, half-siblings and cousins who were all born after 1946. Sensitivity analysis excluding twins from the full-sibling group was also performed. Sex-stratified familial ORs were also calculated. Statistical significance was set at $P < 0.05$, and all tests were two tailed. Data were analysed from December 2021 to February 2022 using SAS version 9.4 (SAS Institute, USA).

Results

Total study population was 6 334 979 persons and consisted of 5 577 449 full-siblings, 1 321 414 half-siblings, and 3 952 137 cousins (*Table 1*). In total, 10 272 (0.16%) unique individuals were diagnosed with DCM and 3769 (0.06%) with HCM. Of these, 7716 (75.12%) and 2375 (63.01%) were males, respectively (*Table S4*).

Familial risk for DCM

Table 2 shows, in the crude Model 1, that DCM risk for full-sibling with affected sibling was increased (OR: 11.91; 95% CI, 10.85–13.07). In multivariable-adjusted Model 2, which also included birth year, sex, and educational attainment, the familial OR for DCM was 5.96 (95% CI, 5.42–6.55). After adjustment for co-morbidities in Model 3, the familial OR was slightly attenuated but still high (5.35; 95% CI, 4.85–5.90). Among half-siblings, the familial OR in the fully adjusted Model 3 was 2.68 (95% CI, 1.86–3.87), and among cousins 1.72 (1.12–2.64). Person-years, incidence rates, and IRR according to relative history of DCM are presented in *Table S5*. The incidence rate of DCM for those with an affected full-sibling was 1.38 (95% CI 1.26–1.51) per 1000 person-years compared with 0.12 (95% CI 0.12–0.12) per 1000 person-years for those without an affected full-sibling. Kaplan–Meier curves according to relative history of DCM are presented in *Figure 1*.

Familial risk for HCM

Table 2 shows, in the crude Model 1, that HCM risk for full-sibling with affected sibling was increased (OR: 74.58; 95% CI, 66.62–83.49). In multivariable-adjusted Model 2, which also included birth year, sex, and educational attainment, the familial risk OR for HCM was 45.64 (95% CI, 40.72–51.15). After adjustment for co-morbidities in Model 3, the familial OR was slightly attenuated but still high (42.44; 95% CI, 37.66–47.82). Among half-siblings, the familial OR in the fully adjusted Model 3 was 32.70 (95% CI, 21.32–50.15), and among cousins 36.96 (29.50–46.31). Person years, incidence rates, and IRR according to relative history of HCM are presented in *Table S6*. The incidence rate of HCM for those with an affected full-sibling was 2.90 (95% CI 2.60–3.23) per 1000 person-years compared with 0.04 (95% CI 0.04–0.04) per 1000 person-years for those without an affected full-sibling. Kaplan–Meier curves according to relative history of HCM are presented in *Figure 2*.

Sensitivity analysis for DCM

Sensitivity analysis for DCM was performed with exclusion of other aetiological causes (*Table S2*). Among full-siblings, ORs were higher. Few cases remained among half-sibling and cousins limiting the interpretation of these data. *Table 3* shows the result, in the crude Model 1, that DCM risk for full-siblings with affected sibling was increased (OR: 16.65; 95% CI, 14.46–19.18). In the multivariable-adjusted Model 2, which also included birth year, sex, and educational attainment, the familial OR for DCM was 9.28 (95% CI, 8.05–10.69). After adjustment for co-morbidities in Model 3, the familial OR was slightly attenuated but still high (8.37; 95% CI, 7.23–9.68). Among half-siblings and among cousins, the familial OR in the fully adjusted Model 3 was 1.58 (95% CI, 0.70–3.56) and 1.88 (95% CI, 1.06–3.35), respectively.

When restricting the analysis to a dataset adapted to cousins born years (all relatives born after 1946), familial ORs in the fully adjusted Model 3 were 7.73 (95% CI 6.59–9.05), 1.89 (95% CI 1.05–3.39), and 1.72 (95% CI 1.12–2.63) among full-siblings, half-siblings, and cousins, respectively (*Table S7*).

Among full-siblings, female sex was associated with higher DCM probability. Among half-sibling no significant sex differences were observed. Among cousins, pairs with opposite sex had lower ORs than male pairs (*Table S8*).

Sensitivity analysis was also performed excluding twins from the full-sibling group with similar results and OR for DCM (*Table S9* and *Figure S1*) compared with *Table 2*, where twins were not excluded from the full-sibling group.

Sensitivity analysis for HCM

Sensitivity analysis for HCM was performed with exclusion of other aetiological causes (*Table S3*). Generally, all familial risks for HCM were higher after exclusions. *Table 3* shows, in the crude Model 1, that HCM risk for full-sibling with affected sibling was increased (OR: 92.19; 95% CI, 81.75–103.95). In multivariable-adjusted Model 2, which also included birth year, sex, and educational attainment, the familial

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Table 1 Characteristics of study population stratified by the degree of family relationship and documented history of DCM or HCM in healthcare registers

	Full-siblings 5 577 449 (100)			
	DCM Participants, no (%)		HCM Participants, no (%)	
Characteristics	Without DCM diagnosis 5 567 940 (99.83)	With DCM diagnosis 9509 (0.17)	Without HCM diagnosis 5 573 975 (99.94)	With HCM diagnosis 3474 (0.06)
Year of birth, median [IQR] (range), y	1973 [1955–1992] (1932–2015)	1948 [1942–1956] (1932–2015)	1973 [1955–1992] (1932–2015)	1949 [1942–1963] (1932–2015)
Age at end of follow-up, median [IQR] (range), y	42 [22–60] (0–83)	65 [57–71] (0–83)	42 [22–60] (0–83)	65 [51–72] (0–83)
Age at DCM onset, median [IQR] (range), y	NA	59 [50–65] (0–83)	NA	58 [45–66] (0–83)
Sex				
Male	2 851 505 (51.21)	7145 (75.14)	2 856 476 (51.25)	2174 (62.58)
Female	2 716 435 (48.79)	2364 (24.86)	2 717 499 (48.75)	1300 (37.42)
Education				
(>11 y)	2 418 639 (43.44)	1958 (20.59)	2 419 593 (43.41)	1004 (28.90)
Source				
Hospital care register	NA	5769 (60.67)	NA	1310 (37.71)
Outpatient register	NA	3740 (39.33)	NA	2164 (62.29)
	Half-siblings 1 321 414 (100)			
	DCM Participants, no (%)		HCM Participants, no (%)	
Characteristics	Without DCM diagnosis 1 319 831 (99.88)	With DCM diagnosis 1583 (0.12)	Without HCM diagnosis 1 320 855 (99.96)	With HCM diagnosis 559 (0.04)
Year of birth, median [IQR] (range), y	1981 [1966–1995] (1932–2015)	1955 [1947–1965] (1932–2014)	1981 [1966–1995] (1932–2015)	1961 [1950–1977] (1932–2015)
Age at end of follow-up, median [IQR] (range), y	33 [20–49] (0–83)	58 [49–66] (0–83)	33 [20–49] (0–83)	53 [37–64] (0–83)
Age at DCM onset, median [IQR] (range), y	NA	52 [42–60] (0–81)	NA	46 [30–58] (0–83)
Sex				
Male	673 331 (51.02)	1162 (73.40)	674 134 (51.04)	359 (64.22)
Female	646 500 (48.98)	421 (26.60)	646 721 (48.96)	200 (35.78)
Education				
(>11 y)	433 298 (32.83)	241 (15.22)	433 394 (32.81)	145 (25.94)
Source				
Hospital care register	NA	958 (60.52)	NA	220 (39.36)
Outpatient register	NA	625 (39.48)	NA	339 (60.64)
	Cousins 3 952 137 (100)			
	DCM Participants, no (%)		HCM Participants, no (%)	
Characteristics	Without DCM diagnosis 3 950 254 (99.95)	With DCM diagnosis 1883 (0.05)	Without HCM diagnosis 3 951 082 (99.97)	With HCM diagnosis 1055 (0.03)
Year of birth, median [IQR] (range), y	1987 [1973–2000] (1947–2015)	1967 [1962–1975] (1950–2015)	1987 [1973–2000] (1947–2015)	1975 [1965–1992] (1951–2015)
Age at end of follow-up, median [IQR] (range), y	28 [15–41] (0–68)	47 [38–53] (0–65)	28 [15–41] (0–68)	39 [22–49] (0–64)
Age at DCM onset, median [IQR] (range), y	NA	41 [32–48] (0–63)	NA	32 [16–44] (0–63)
Sex				
Male	2 028 974 (51.36)	1387 (73.66)	2 029 669 (51.37)	629 (65.59)
Female	1 921 280 (48.64)	496 (26.34)	1 921 413 (48.63)	363 (34.41)

(*Continues*)

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Table 1 (continued)

	Cousins 3 952 137 (100)			
	DCM Participants, no (%)		HCM Participants, no (%)	
Characteristics	Without DCM diagnosis 3 950 254 (99.95)	With DCM diagnosis 1883 (0.05)	Without HCM diagnosis 3 951 082 (99.97)	With HCM diagnosis 1055 (0.03)
Education (>11 y)	1 933 111 (48.94)	439 (23.31)	1 933 115 (48.93)	435 (41.23)
Source				
Hospital care register	NA	1118 (59.37)	NA	332 (31.47)
Outpatient register	NA	765 (40.63)	NA	723 (68.53)

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; NA, not applicable.
Range, (min–max).

OR for HCM was 59.53 (95% CI, 52.72–67.22). After adjustment for co-morbidities in Model 3, the familial OR was slightly attenuated but still high (55.70; 95% CI, 49.07–63.23). Among half-siblings, the familial OR in the fully adjusted Model 3 was 46.29 (95% CI, 30.08–71.22), and among cousins 40.50 (32.17–50.99).

When restricting the analysis to a dataset adapted to cousins born years (all relatives born after 1946), familial ORs in the fully adjusted Model 3 were 151.22 (95% CI 131.09–174.43), 60.64 (95% CI 37.46–98.17), and 36.96 (95% CI 29.50–46.31) among full-siblings, half-siblings, and cousins, respectively (*Table S7*).

Among full-siblings, half-siblings, and cousins, female sex was associated with higher HCM probability compared with pairs with opposite sex and males. Among half-siblings and cousins, male pairs were associated with lower probability of HCM than pairs with opposite sex (*Table S8*).

Sensitivity analysis was also performed excluding twins from the full-sibling group with similar results and OR for HCM (*Table S9* and *Figure S1*) compared with *Table 2*, where twins were not excluded from the full-sibling group.

Discussion

In this nationwide family study, we identified strong hereditary components of both DCM and HCM with distinctly higher impact of heritability for HCM. The familial association was independent of traditional cardiovascular risk factors and clinically relevant co-morbidities. The strongest aggregations of DCM and HCM were observed in pairs of full-siblings, whereas this association, although significant, was distinctly attenuated among half-siblings and cousin pairs. As the familial risk factors and associations correlated with genetic resemblance, this confirms the well-established genetic nature of DCM and HCM being present in cases derived from the general population. Although the yield and possible clinical benefit of genetic testing have not been established in our study, familial aggregation data substantiate guidelines recommendation[30] that at diagnosis, probands should be informed about high familial risks and first-degree and close relatives of affected individuals should undergo cascade clinical screening because clinical detection of disease can prompt prophylactic and therapeutic interventions, regardless of genetic results.[31] Noticeably, HCM is the most common cause of sudden death in young athletes,[32] with most cases occurring in previously undiagnosed individuals,[33] highlighting the need for early diagnosis[34] and complementary preventive strategies.

Studying family aggregation of phenotype is an important part of a systematic approach to the identification of genetic determinants in complex diseases.[35] The family relationship studies create a unique possibility to explore genetic and non-genetic familial factors by observing occurrence of specific phenotypes among first-degree, second-degree, and third-degree relatives. First-degree relatives share 50% of their genes, in addition to environmental exposure common to their family. Second-degree relatives (e.g. half-siblings) share 25% of their genes, and third-degree relatives (e.g. first cousins) share 12.5% of their genes.[35] In this study, the probability of DCM and HCM among relatives of affected individuals followed a pattern of increasing risk of cardiomyopathy occurrence along with the grade of relationship, being highest in full-siblings. As third degree-relatives usually do not share household environment, these results speak in favour of mainly genetic components of cardiomyopathy aetiology. Furthermore, common risk variants co-inherited with the Mendelian genetic defect could modulate disease susceptibility with polygenic contributions explaining a significant proportion of inter-individual differences in HCM disease severity[36] and earlier disease onset observed among relatives.[37]

Our estimates of DCM (0.16%) and HCM (0.06%) prevalence are consistent with previous reports from the general population.[2,3,8,38] Epidemiological studies are usually performed on the basis of fully penetrant disease, largely based on the presence of overt HCM phenotype by imaging (LV hypertrophy ≥15 mm), whereas in most families with HCM the majority of individuals with pathogenetic variants

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Table 2 Risk of DCM or HCM in family members stratified by the degree of relationship and documented history of DCM or HCM among relatives

Full-sibling								
	DCM (n = 9 863 836) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 9 863 836) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3	
Full-sibling not affected	1[Reference]	1[Reference]	1[Reference]	19 525/9 843 849	1[Reference]	1[Reference]	1[Reference]	6622/9 856 882
Full-sibling affected	11.91 (10.85–13.07)	5.96 (5.42–6.55)	5.35 (4.85–5.90)	462/19 987	74.58 (66.62–83.49)	45.64 (40.72–51.15)	42.44 (37.66–47.82)	332/6954
Half-sibling								
	DCM (n = 2 723 887) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 2 723 887) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3	
Half-sibling not affected	1[Reference]	1[Reference]	1[Reference]	3449/2 720 406	1[Reference]	1[Reference]	1[Reference]	1104/2 722 759
Half-sibling affected	7.32 (5.16–10.38)	2.98 (2.10–4.24)	2.68 (1.86–3.87)	32/3481	53.70 (35.70–80.78)	32.96 (21.82–49.80)	32.70 (21.32–50.15)	24/1128
Cousin								
	DCM (n = 24 789 657) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 24 789 657) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3	
Cousin not affected	1[Reference]	1[Reference]	1[Reference]	12 933/24 776 702	1[Reference]	1[Reference]	1[Reference]	7067/24 782 508
Cousin affected	3.68 (2.51–5.41)	1.80 (1.19–2.74)	1.72 (1.12–2.64)	22/12 955	40.68 (32.68–50.64)	35.09 (28.18–43.69)	36.96 (29.50–46.31)	82/7149

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.
Mode1 1 unadjusted. Model 2 adjusted for birth year, sex, and education. Model 3 furthermore adjusted for coronary heart disease, hypertension, atrial fibrillation, diabetes, aortic stenosis, chronic obstructive pulmonary disease, and cancer. All calculations are based on double entry.

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Figure 1 Dilated cardiomyopathy. Kaplan–Meier curves for cardiomyopathy-free survival by family history of dilated cardiomyopathy (DCM) among relatives and degree of family relationship. (A) full-siblings; (B) half-siblings; (C) cousins.

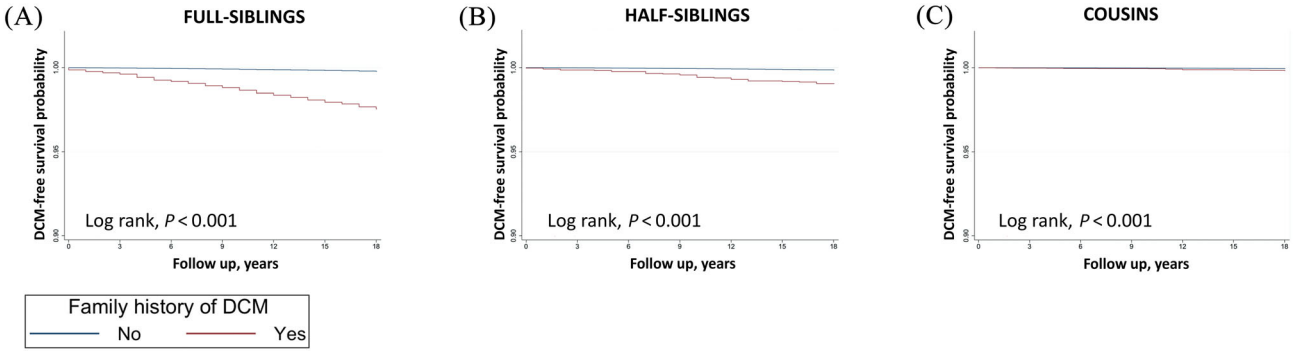
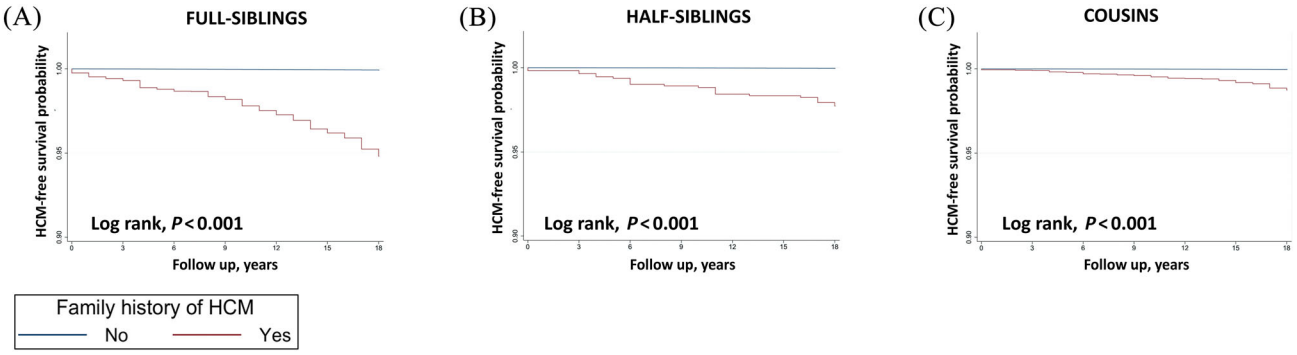


Figure 2 Hypertrophic cardiomyopathy. Kaplan–Meier curves for cardiomyopathy-free survival by family history of hypertrophic cardiomyopathy (HCM) among relatives and degree of family relationship. (A) full-siblings; (B) half-siblings; (C) cousins.



do not fulfil the conventional diagnostic criteria.[3] This likely explains why our data may underestimate true genetic prevalence of subclinical HCM phenotypes, which is also strongly influenced by screening method. Indeed, use of cardiovascular magnetic resonance increases the yield of early phenotype detection,[39,40] providing mass and wall-thickness measurements that are more precise and reproducible compared with echocardiography,[41] particularly for some segments (basal anterior or lateral or apical), and unlocks identification of phenocopies by tissue characterization modules.[42,43]

Sex-based difference was present in previous studies to a similar degree,[3,10,38,44] with male predominance ranging between 1.5:1 and 2:1 in both HCM and DCM. This might be partially explained by wall thickness or LV size not being adjusted to sex or body size,[38] lower disease penetrance in women,[45] mode of inheritance, and/or delayed disease onset secondary to genetic and endocrine factors directly impacting phenotypic expression.[46] In our cohort, relatives of affected females were found more likely to be affected than relatives of affected males, suggesting the possibility of a multifactorial threshold model of inheritance by which individuals of the less commonly affected sex carry a higher genetic load and are therefore more likely to transmit the disease to the offspring and have siblings with the disease.[47] In this view, females require a greater number of, or more potent, susceptibility genes than males to inherit and express the phenotype and therefore would be predicted to have a higher rate of transmission of the cardiac disease. This is known as the Carter effect,[48] a multifactorial threshold model with sex dimorphism for liability,[49] that in our study appears largely more evident for HCM.

Notably, an increasing body of data indicates that sex has distinct prognostic implications, with men being at higher risk of adverse events in the context of titin[50] and lamin A/C cardiomyopathy,[51] and women with HCM showing higher risk of progression to advanced heart failure or death, often associated with outflow obstruction.[52]

A number of germline variants involved in heart muscle disorders, such as nuclear envelopathies and

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Table 3 Sensitivity analysis: risk of DCM or HCM in family members stratified by the degree of relationship and documented history of DCM or HCM among relatives

Full-sibling								
	DCM (n = 9 846 248) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 9 861 764) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3[a]		Model 1	Model 2	Model 3[b]	
Full-sibling not affected	1[Reference]	1[Reference]	1[Reference]	10 862/9 835 186	1[Reference]	1[Reference]	1[Reference]	5605/9 855 865
Full-sibling affected	16.65 (14.46–19.18)	9.28 (8.05–10.69)	8.37 (7.23–9.68)	200/11 062	92.19 (81.75–103.95)	59.53 (52.72–67.22)	55.70 (49.07–63.23)	294/5899
Half-sibling								
	DCM (n = 2 721 137) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 2 723 635) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3[a]		Model 1	Model 2	Model 3[b]	
Half-sibling not affected	1[Reference]	1[Reference]	1[Reference]	2087/2 719 044	1[Reference]	1[Reference]	1[Reference]	978/2 722 633
Half-sibling affected	3.74 (1.68–8.35)	1.75 (0.79–3.91)	1.58 (0.70–3.56)	6/2093	68.29 (45.33–102.88)	46.01 (30.43–69.58)	46.29 (30.08–71.22)	24/1002
Cousin								
	DCM (n = 24 782 087) OR (95% CI)			Cases, no./ persons at risk, no.	HCM (n = 24 788 767) OR (95% CI)			Cases, no./ persons at risk, no.
Variable	Model 1	Model 2	Model 3[a]		Model 1	Model 2	Model 3[b]	
Cousin not affected	1[Reference]	1[Reference]	1[Reference]	9153/24 772 922	1[Reference]	1[Reference]	1[Reference]	6624/24 782 065
Cousin affected	3.57 (2.03–6.28)	2.07 (1.18–3.65)	1.88 (1.06–3.35)	12/9165	44.13 (35.26–55.22)	38.82 (31.01–48.61)	40.50 (32.17–50.99)	78/6702

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.
Model 1 unadjusted. Model 2 adjusted for birth year, sex, and education. Patients with potential etiological differential diagnoses were excluded: Exclusion diagnoses for DCM: coronary heart disease, hypertensive heart disease, myocarditis, valvular heart disease, peripartum cardiomyopathy, sarcoidosis, alcoholic cardiomyopathy, cardiomyopathy due to drugs and other external agents, and cardiomyopathy in diseases classified elsewhere. Exclusion diagnoses for HCM: hypertensive heart disease, aortic stenosis, amyloidosis, other sphingolipidosis (e.g. Fabry's disease), early-onset cerebellar ataxia (Friedreich ataxia), and myotonic disorders (myotonic dystrophy).
[a]Model 3 furthermore adjusted for hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary, and cancer disease.
[b]Model 3 furthermore adjusted for coronary heart disease, hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary, and cancer disease. All calculations are based on double entry.

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sarcomeropathies, have been recognized among adult and paediatric patients to increase susceptibility not only for cancer therapy-related cardiac dysfunction[53] and peripartum cardiomyopathy[54] but also for development of different types of cancer, depicting a complex interplay between environmental and hereditary factors participating in the development of cardiomyopathies and predisposition to cancer,[55] which makes it important to take cancer into account in modern epidemiological analyses on cardiomyopathies.

Strengths and limitations

The large size and nationwide coverage of the study sample are a strength. Other important strengths include the use of validated national hospital discharge data,[21–25] which allows for elimination of recall bias, and the capability of controlling for major confounders, such as cardiovascular risk factors, aortic stenosis, atrial fibrillation and cancer. Further, Swedish registers such as the national statistical register and the Swedish Hospital Discharge Register have high coverage and high data validity.[21,28,29] A further strength is that the ICD-10 cardiomyopathy has been specifically validated.[28,29]

A limitation is the lack of biomarkers, ethnicity, genetic, and genomic information. For instance, in familial studies, there is always the issue of assurance of paternity.[56] However, a recent Swedish study shows that among offspring born 1950 and later, the frequency of misattributed paternity in Sweden is low (1.7%) and has decreased to 1%. Another limitation is that the study was limited to Sweden. However, the Swedish population resembles many other Caucasian populations of European origin. Further possible limitations include the changing diagnostic criteria for DCM and HCM over time, application of diagnostic techniques has also altered over time, and we had no access to the original diagnostic investigations.

Conclusions

Familial risk of DCM and HCM among relatives of affected individuals depends on the degree of relationship, being strongest in full-siblings but still significant in second-degree and third-degree relatives. This supports the idea that genetic components of DCM and HCM exist in those cases where current genetic testing is incapable of major gene identification and that more complex genetic backgrounds may operate behind cardiomyopathy susceptibility. The finding of a Carter effect, more pronounced in HCM, suggests a multifactorial threshold model of inheritance. The familial risks are high, and clinical screening of first-degree and other close relatives of affected patients is likely to be worthwhile, and further genetic association studies are motivated to improve our understanding of the epidemiology of inherited cardiomyopathies.

Conflict of interest

AF has received speaker fees from Medtronic Inc., Biotronik, and Bristol-Myers Squibb and is consultant to Medtronic Inc. and Argenx BV. RS is a consultant to Medtronic Inc., a member of the speakers' bureau of Abbott (SJM) Laboratories Corp. and a shareholder in Edwards Lifesciences Corp. and Boston Scientific Corp. No other disclosures were reported.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The distribution of ICD 10 I42x diagnoses was collected according to the first-ever diagnosis from hospital discharge and outpatient care registers for the period from 1997 to 2015.
Table S2. Exclusions criteria for DCM (dilated cardiomyopathy) used in the sensitivity analysis.
Table S3. Exclusions criteria for HCM (hypertrophic cardiomyopathy) used in the sensitivity analysis.
Table S4. Baseline characteristics by the degree of family relationship and history of DCM or HCM in Health Care Registers.
Table S5. Person years, incidence rates, and incidence rate ratio (IRR) for DCM. Based on double entry.
Table S6. Person years, incidence rates, and incidence rate ratio (IRR) for HCM. Based on double entry.
Table S7. Risk of DCM or HCM in family members stratified by

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the degree of relationship and documented history of DCM or HCM among relatives based on adapted dataset to cousins born years (full-siblings, half-siblings and cousins all born after 1946).

Table S8. Risk of DCM or HCM in family members stratified by the degree of relationship, documented history of DCM or HCM among relatives and sex.

Table S9. Risk of DCM or HCM in family members stratified by the degree of relationship and documented history of DCM or HCM among relatives with exclusion of all twins from the full-sibling group.

Figure S1. Kaplan–Meier curves for cardiomyopathy-free survival stratified by family history of dilated cardiomyopathy (DCM, panel A) and family history of hypertrophic cardiomyopathy (HCM, panel B) with the exclusion of all twins from the full-sibling cohort.

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