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Incidence rates of dilated cardiomyopathy in adult first-degree relatives versus matched controls

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ABSTRACT

Background: The incidence rates and importance of traditional risk factors in dilated cardiomyopathy among first-degree relatives are unknown.
Methods and Results: We identified all probands with dilated cardiomyopathy (n = 13,714, mean age at diagnosis 63 years) from the Danish nationwide registries between 1994 and 2017. Incidence rates among first-degree relatives (n = 29,671, mean age 38 years) and for up to 10 age- and sex-matched controls were calculated. Totally 233 (0.8%) first-degree relatives and 285 (0.1%) controls developed dilated cardiomyopathy during a median follow-up of 8.2 (Q1-Q3 4.4–13.3) years. Incidence rates (per 100,000 person-years) were 86.4 (95% confidence interval 73.9–101.0) and 111.1 (79.4–128.7) for first-degree relatives aged < 50 and ≥ 50 years, respectively, versus 7.5 (6.4–8.9) and 19.7 (16.8–23.2) for controls. Atrial fibrillation, diabetes, ischemic heart disease, and hypertension were associated with increased risks of developing dilated cardiomyopathy both in first-degree relatives and controls. Population attributable fractions for the 4 risk factors were 27.7% for first-degree relatives and 37.3% for controls aged < 50 years, and 46.4% versus 58.4% for first-degree relatives and controls among people aged ≥ 50 years, respectively.
Conclusions: The absolute incidence rates of dilated cardiomyopathy in first-degree relatives to patients with dilated cardiomyopathy were low, but significantly higher than in matched controls and elevated by the presence of additional risk factors, especially atrial fibrillation. Additional investigations are warranted to assess whether aggressive treatment of risk factors translates into a reduction of dilated cardiomyopathy in first-degree relatives.

1. Introduction

Dilated cardiomyopathy, one of the most common forms for inherited cardiomyopathy, has a variable penetrance that is incompletely understood. In particular, the potential contributions of standard risk factors (diabetes, hypertension, atrial fibrillation, and ischemic heart disease) to a genetic (familial) susceptibility for the risk of developing cardiomyopathy have not been well characterized. Notably, the incidence rates of dilated cardiomyopathy have increased over the past few decades in the community among younger adults [1]. Since genetic variation has not changed over such a short period, this observation suggests that non-genetic factors may contribute to risk of developing

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dilated cardiomyopathy in predisposed individuals [2,3]. Supporting this notion, hypertensive disorders in pregnancy and adolescent obesity have been linked to the development of cardiomyopathy in midlife [4,5]. Similar, patients who have a familial predisposition to cardiomyopathy and heart failure have higher rates of heart failure if they develop atrial fibrillation compared with controls [6]. Recent studies have also shown that approximately 10% of patients who develop cardiomyopathy after chemotherapy, during the peripartum period, or after excessive alcohol intake (alcoholic cardiomyopathy) harbor mutations in dilated cardiomyopathy-associated genes (such as rare titin truncated [TTN] variants), lending further support to the hypothesis that dilated cardiomyopathy may develop in the presence of additional risk factors (cardiac stressors) [7–9].

In the present study, we aimed to investigate the incidence rates of dilated cardiomyopathy in individuals with and without a first-degree relative with dilated cardiomyopathy, and to estimate the impact of diabetes, hypertension, atrial fibrillation, and ischemic heart disease on the disease risk in familial predisposed individuals.

2. Methods

The Danish nationwide family registry holds data on all parents of children born after 1953. By linkage of this registry with the Danish patient registry, we identified all probands with a diagnosis of dilated cardiomyopathy (ICD-10 code I42.0) between 1994 and 2017. First-degree relatives (i.e., their siblings and children) were matched with up to 10 controls on birth year and sex, using the risk-set principle. Controls were followed for the risk of developing incident dilated cardiomyopathy from the date of their matched case (i.e., the date of dilated cardiomyopathy diagnosis in the case's proband) until the first occurring of Dec 31, 2017, emigration, or death. As a sensitivity analysis, we also estimated the risk of developing heart failure.

2.1. Definition and validity of diagnostic codes

All diagnoses made at Danish hospitals are registered at the time of contact and include both hospitalized and ambulatory (clinic) patients. All Danish citizens are assigned a personal identification number at time of birth or immigration, which makes them eligible to use the universal, taxfunded health care system (at no personal co-payment) regardless of factors such as employment status. The personal identification number is used for all health-care contacts and enables linkage of various registries. All diagnoses have since 1994 been registered according to the International Classification System of Diseases (ICD) version 10. The registry was initiated in 1978 and up until 1993 the ICD version 8 was used. The dilated cardiomyopathy diagnosis has previously been validated in the used registries, with a positive predictive value ranging between 75% and 86% based on limited samples [10,11]. Additionally, we undertook a separate review of all charts with an I42.0 diagnosis at two Danish hospitals (Department of Cardiology, Herlev and Gentofte hospitals) between 2015 and 2018. We found 85 patients of whom 70 had a definitive diagnosis of dilated cardiomyopathy (82% of all) according to the 2008 European Society of Cardiology criteria (dilated left ventricle with an ejection fraction $<$ 45% in the absence of prior chemotherapy, poorly controlled hypertension, significant coronary artery disease or valve disease, prior myocarditis, or substance abuse) [12]. Considering the proposed updated criteria from 2016, we found that 76 patients had dilated cardiomyopathy, corresponding to an accuracy of 89% [13].

Diabetes and hypertension are usually treated by general practitioners and their diagnostic coding system is not available for research. Therefore, in addition to a hospital diagnosis (ICD-10 codes E10-E14 for diabetes, and I10-15 for hypertension), we used antidiabetic treatment as a proxy for diabetes and the use of at least 2 antihypertensive agents as a proxy for hypertension. The latter proxy for hypertension has been validated with a positive predictive value of 80% for the presence of hypertension [14]. All other diagnoses, including atrial fibrillation (I48), ischemic heart disease (I20-I25), and heart failure (I50, I110) have been validated with excellent positive predictive values [11,15].

2.2. Study design

We followed all adult individuals aged $\geq$ 20 years from the date when their first-degree relative was diagnosed with dilated cardiomyopathy (and corresponding date for controls) for incident dilated cardiomyopathy, defined as a new diagnosis of I42.0. For sensitivity, we also investigated the risk of developing any heart failure (ICD-10 I50, I110).

2.3. Statistical analysis

Tests for differences in baseline characteristics of individuals with a first-degree relative with dilated cardiomyopathy and controls were done by calculation of standardized differences as well as by the Wilcoxon ranked sum test and the Chi-squared test, respectively. We calculated hazards ratios for dilated cardiomyopathy associated with baseline risk factors in individuals with and without a first-degree family-member by multivariable Cox regression models. The proportional hazards assumption was checked and met. We tested for differences in hazards ratios associated with risk factors by inclusion of an interaction term in models (relative status * risk factor). Given the young age at baseline (and therefore low prevalence of risk factors at baseline) additional analyses were performed as time-dependent models, where risk factors and age were updated continuously throughout follow-up. We calculated population attributable fractions as (incidence rate in total population - incidence rate in non-exposed) / (incidence rate in total population) $\times$ 100 based on the estimates from the time-dependent analyses. All analyses were undertaken in SAS version 9.4 (SAS institute, Cary, NC). Two-sided p-values $<$ 0.05 were considered statistically significant.

2.4. Ethical considerations

Being observational in nature and using de-identified individuals, the study was exempted from ethical approval. The study was approved by the Danish Data Protection Agency.

3. Results

A total of 13,714 probands were identified (7746 fathers, 3179 mothers, and 2789 siblings). Their median age was 62.5 (Q1-Q3 53.0–71.5) years at first diagnosis. Characteristics of probands are available in online supplemental Table 1. We successfully matched 29,671 first-degree dilated cardiomyopathy relatives with 295,864 controls. Details on the cohort selection are available in online supplemental Fig. 1 (flow chart diagram). The median age of the study sample at baseline was 38.2 (Q1-Q3, 28.7–46.0) years and approximately half were women, Table 1. Relatives of patients with dilated cardiomyopathy had a slightly higher prevalence of atrial fibrillation (0.5% vs. 0.4%), and more likely to have hypertension, diabetes, and ischemic heart disease, although the overall prevalence of these diseases was low (Table 1).

3.1. Occurrence of dilated cardiomyopathy

During a median follow-up of 8.2 (Q1-Q3 4.4–13.3) years, 233 first-degree relatives (0.8%) and 285 (0.1%) controls were diagnosed with dilated cardiomyopathy. The median age at the time of dilated cardiomyopathy diagnosis was 5 years lower in first-degree relatives with dilated cardiomyopathy than in matched controls (44.1 [Q1-Q3, 34.5–50.8] vs. 49.2 [44.3–54.5] years, p $<$ 0.0001). Adjusted for age and sex, hazards ratio for developing dilated cardiomyopathy among

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Table 1
Baseline characteristics of the study sample.

	First-degree relative with dilated	Controls	Standardized difference
N	29,671	295,864	
Age, years (median, Q1-Q3)	38.2 (28.8–46.1)	38.2 (28.7–46.0)	0.0018
Sex, female	14,000 (47%)	139,355 (47%)	−0.0017
Atrial fibrillation	148 (0.5%)	1201 (0.4%)	0.014
Hypertension	1091 (3.6%)	8502 (2.9%)	0.040
Diabetes	775 (2.6%)	6651 (2.3%)	0.024
Ischemic heart disease	326 (1.1%)	2641 (0.9%)	0.021
Paternal proband	17,806 (60%)		
Maternal proband	7201 (24%)		
Sibling proband	4664 (16%)		
Proband < 50 years of age at time of diagnosis	5449 (18%)		

Footnote: * refers to either diabetes, hypertension, or ischemic heart disease.

first-degree relatives compared with controls was 8.21 (95% confidence interval [CI] 6.91–9.76]). This risk estimate was unchanged by additional adjustment for prevalent diabetes, ischemic heart disease, hypertension, and atrial fibrillation (hazards ratio 8.11 [95% CI 6.82–9.64]). The hazards ratios for dilated cardiomyopathy (compared with controls) were greater when the proband was younger at time of dilated cardiomyopathy diagnosis: 16.71 (13.10–21.31) vs. 8.27 (6.66–10.28) vs. 3.07 (95% CI 2.09–4.52) for proband ages < 50 years, 50–70 years, and > 70 years, respectively. The risks of developing dilated cardiomyopathy were higher if the proband was a mother (hazards ratio 10.57 [8.17–13.66]) or a sibling (13.70 [10.45–17.98]) than a father with dilated cardiomyopathy (hazards ratio 5.50 [4.35–6.95]). Stratifying by sibling sex, the risks were numerically greater if the sibling with dilated cardiomyopathy was a female (hazards ratio 19.17 [12.28–29.92]) than a male (hazards ratio 12.11 [8.82–16.61], p for difference 0.08). Similar, the hazards ratios were numerically greater for females than males, if they had a first-degree relative with dilated cardiomyopathy (11.8 [8.53–16.3] versus 6.97 [5.67–8,57], p for difference 0.007). Crude incidence rates stratified by age and risk factors at baseline are presented in Fig. 1 (details of numbers of events by age-group and total follow-up are available in online supplemental Table 2). Diabetes and hypertension conferred relatively smaller hazards ratios among individuals with a first-degree relative with dilated cardiomyopathy compared to controls, p for interactions between risk factor and familial predisposition ≤ 0.02, online supplemental Fig. 2.

3.2. Occurrence of heart failure

Totally 418 and 1630 individuals with a first-degree family member with dilated cardiomyopathy and controls developed all-cause heart failure during follow-up. Crude incidence rates by age-groups and risk factors are available in Fig. 1 C and D. Adjusted for age and sex, individuals with a first-degree degree family member with dilated cardiomyopathy had a hazards ratio of 2.59 (95% CI 2.32–2.88) for developing all-cause heart failure. Multivariable adjustment did not alter the estimates (hazards ratio 2.52, 95% CI 2.26–2.81). As for the dilated cardiomyopathy outcomes, hypertension and ischemic heart disease tended to be of stronger relative importance in people without vs. with a first-degree relative with dilated cardiomyopathy, online supplemental Fig. 3.

3.3. Time-dependent analyses

During follow-up, more individuals with familial dilated cardiomyopathy developed risk factors compared with controls, Table 2. Particularly the risk of developing atrial fibrillation was increased; age and sex-adjusted hazards ratio 1.54, 95% CI 1.39–1.71. After adjustment for risk factors occurring throughout follow-up, first degree relatives had an adjusted-hazards ratio of 7.47 (6.21–9.00) for developing dilated

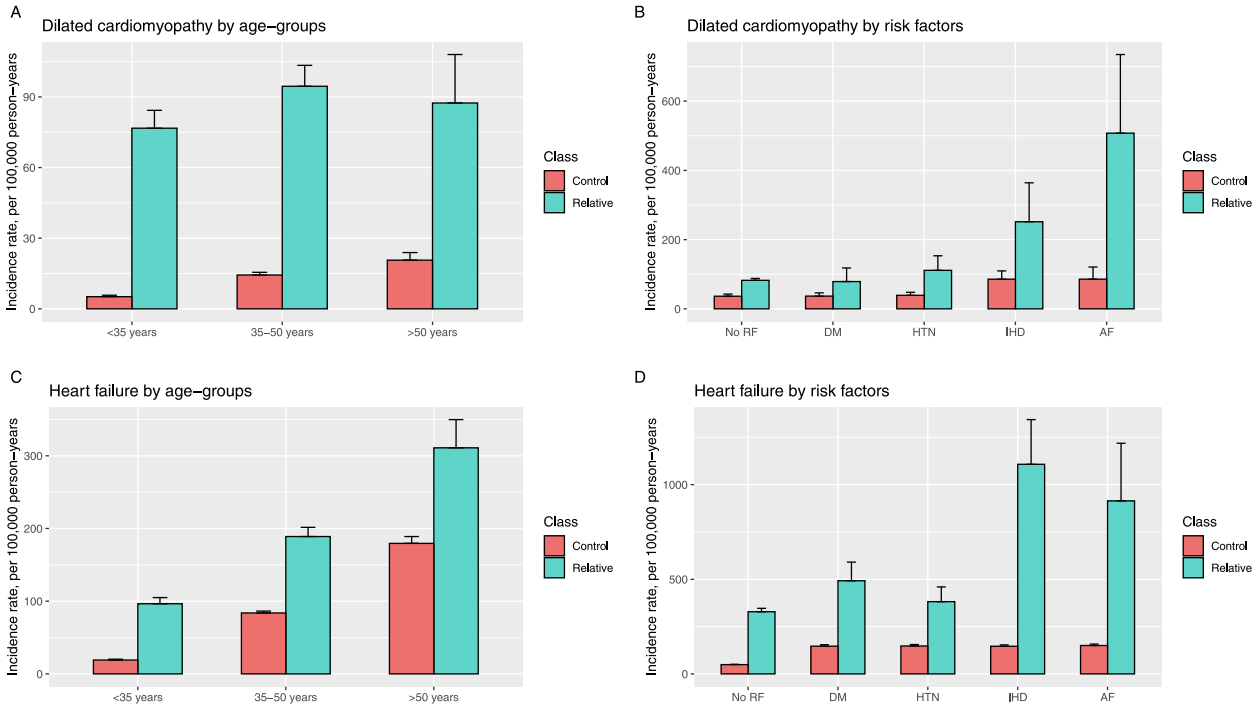

Fig. 1. Incidence rates of dilated cardiomyopathy and heart failure in different age- and risk factor groups Legend: Upper panels of the figure show the incidence rates of dilated cardiomyopathy by age (A) and risk factor groups (B), and lower panels the incidence rates of heart failure by age (C) and risk factor groups (D). AF, atrial fibrillation; DM, diabetes; HTN, hypertension; IHD ischemic heart disease. Error bars represent standard errors of the estimates. Numbers of events and total follow-up time are available in Online supplemental material.

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Table 2
Incidence rates of the development of risk factors in first-degree relatives of patients with dilated cardiomyopathy and controls during follow-up.

	First-degree relatives with dilated cardiomyopathy		Controls		
	Number of incident cases / observational time (1000 person-years)	Incidence rates (95% confidence intervals), per 1000 person-years	Number of incident cases / observational time (1000 person-years)	Incidence rates (95% confidence intervals), per 1000 person-years	Hazards ratio for 1st degree relatives vs. controls (sex and age-adjusted)
Atrial fibrillation	399 / 268.1	1.5 (1.3–1.6)	2608 / 2685.9	1.0 (0.9–1.0)	1.54 (1.39–1.71)
Diabetes	1017 / 261.3	3.9 (3.7–4.1)	8659 / 2621.2	3.3 (3.2–3.4)	1.18 (1.11–1.26)
Hypertension	1841 / 255.4	7.2 (6.9–7.5)	13,562 / 2586.7	5.2 (5.2–5.3)	1.39 (1.32–1.46)
Ischemic heart disease	663 / 265.8	2.5 (2.3–2.7)	4721 / 2665.8	1.8 (1.7–1.8)	1.42 (1.31–1.54)

cardiomyopathy, with greater hazards ratios for young adults vs. middle-aged, 10.06 (7.89–12.82) vs. 4.79 (3.55–6.46) if < 50 years vs. ≥ 50 years of age, p for difference < 0.0001.

The incidence rates of dilated cardiomyopathy in first-degree relatives appeared to plateau after ~ 50 years of age (Fig. 1). Therefore, we stratified subsequent analyses according to an age < 50 or ≥ 50 years of age, respectively. For both individuals with a first-degree relative with dilated cardiomyopathy and controls, the incidence rates of dilated cardiomyopathy were greater in the presence of risk factors, and highest for first-degree relatives with concomitant atrial fibrillation (incidence rate 1.3 per 100 person-years among those < 50 years of age), online supplemental Table 3. The associated risks for a given risk factor tended to be of greater relative importance in younger individuals vs. older, Table 3. Consistent with the non-time-dependent analyses, the relative importance of ischemic heart disease and hypertension was greater among people without vs. with a first-degree family member with dilated cardiomyopathy, Table 3.

The population attributable fractions associated with risk factors are shown in Fig. 2 (numbers are available in online supplemental Table 4). The four risk factors were collectively associated with population attributable fractions of 27.7% (first degree relatives) and 37.3% (controls) for individuals < 50 years, and 46.4% and 58.4% (first degree relatives and controls) for people aged ≥ 50 years, respectively.

For the development of heart failure, a similar relation between risk factors, age, and familial predisposition was noted (online supplemental Tables 5–7) with overall lower hazards ratios associated with risk factors in older individuals versus young, and individuals with versus without a relative with dilated cardiomyopathy. The population attributable fractions associated with the risk factors were greater for heart failure than for dilated cardiomyopathy, Fig. 2B.

3.4. Sensitivity analyses

We also performed analyses restricted to probands without a concomitant diagnosis of ischemic heart disease to rule out any potential misclassification of ischemic cardiomyopathy. Essentially similar results were obtained: first-degree relatives of a patient with dilated cardiomyopathy had a multivariable-adjusted hazards ratio of 9.17 (95% CI 7.65–10.98) for the risk of developing dilated cardiomyopathy after adjustment for baseline variables, and 7.01 (5.74–8.55) after adjustment for variables during follow-up. The risks of developing hypertension (hazards ratio 1.36 [95% CI 1.29–1.44]), diabetes (1.17 [1.09–1.26]), atrial fibrillation (1.70 [1.52–1.91]), and ischemic heart disease (1.41 [1.28–1.54]) during follow-up were increased in first-degree relatives compared to controls (p all < 0.0001). Among first-degree relatives < 50 years, the population attributable fractions were 10.3% for atrial fibrillation, 0.9% for diabetes, 15.9% for hypertension, 6.3% for ischemic heart disease, and 29.1% for all four risk factors. For individuals aged ≥ 50 years, corresponding percentages were 22.2% (atrial fibrillation), 2.5% (diabetes), 15.8% (hypertension), 12.2% (ischemic heart disease), and 46.1% (for all four risk factors). Full incidence rates and calculations of population attributable fractions are available in online supplemental Table 8 and 9.

4. Discussion

Our nationwide study aimed to address three key questions regarding the epidemiology of dilated cardiomyopathy. First, we sought to provide contemporary estimates of the incidence rates of dilated cardiomyopathy in adults with a first-degree relative with dilated cardiomyopathy versus matched controls and quantitate variations in risk estimates by age of onset and sex of probands. The first conclusion is that although the relative risks were increased by approximately 8-fold for first-degree family members, the absolute incidence rates were overall low (<1 per 1,000 person-years in the absence of other risk factors). Second, we observed that the risks of both dilated cardiomyopathy and heart failure were substantially accentuated by the presence of additional risk factors, especially atrial fibrillation, ischemic heart disease, and hypertension. As discussed later, surveillance for these factors in relatives of patients with dilated cardiomyopathy could be important because they may serve as additional key risk markers. Third, atrial fibrillation, ischemic heart disease, hypertension, and diabetes may explain up to a third of the dilated cardiomyopathy cases and nearly half heart failure events occurring among first-degree relatives of patients with dilated cardiomyopathy, and up to two thirds of dilated cardiomyopathy and heart failure cases among controls. We observed that the hazards ratios of developing dilated cardiomyopathy was greater for female first degree relatives than their male counterparts. Similar, individuals who had a mother or sister with dilated cardiomyopathy had greater hazards ratios than individuals who had a father or brother with

Table 3
Hazards ratio estimates based on presence of risk factors for dilated cardiomyopathy, time-dependent analyses.

	Age < 50 years		Age ≥ 50 years	
	1st degree relatives	Controls	1st degree relatives	Controls
Numbers of incident dilated cardiomyopathy	158	138	147	75
Hazards ratios				
Atrial fibrillation	10.81 (5.91–19.79)	5.43 (2.52–11.67)	9.97 (5.45–18.22)	8.10 (5.06–12.97)
Diabetes	0.77 (0.31–1.95)*	1.94 (1.05–3.59)*	0.95 (0.40–2.27)	1.18 (0.68–2.02)
Hypertension	2.80 (1.61–4.88)*	6.32 (3.77–10.60)*	1.44 (0.77–2.69)*	2.98 (1.95–4.55)*
Ischemic heart disease	4.40 (2.18–8.88)*	6.96 (3.82–12.68)*	1.71 (0.79–3.69)*	3.04 (1.89–4.90)*

Footnote: * denotes p-value for interaction < 0.05.

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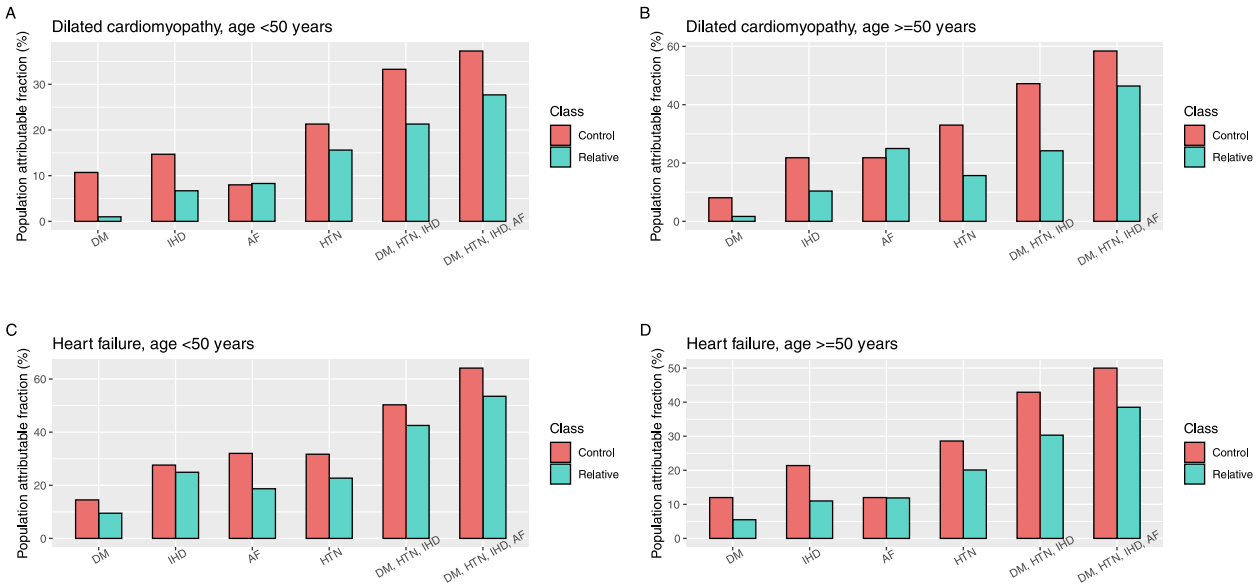

Fig. 2. Population attributable fractions of dilated cardiomyopathy and heart failure according to prevalence of risk factors, time-dependent analyses Legend: Population attributable fractions of dilated cardiomyopathy (A, B) and heart failure (C, D) associated with various risk factors in individuals below or above 50 years of age. AF, atrial fibrillation; DM, diabetes; HTN, hypertension; IHD ischemic heart disease.

dilated cardiomyopathy. Whether this may be related to differences in genetic variation in male versus female first-degree relative or relate to the baseline risk of cardiomyopathy in the community (i.e., a greater baseline risk often translates into a lower relative risk associated with any risk factors) warrants further studies.

4.1. Comparison with other studies

The overall incidence rates in our study population corresponds very well with prior estimates (1–7.5 per 100,000 person-years) [16–19], and are also similar to estimates based on prior autopsy data and screening of hospital records with case ascertainment by echocardiography [20,21]. First-degree relatives to individuals with premature death from cardiomyopathy have previously been shown to have a substantially increased risk of developing cardiomyopathy themselves [22], but to the best of our knowledge, more comprehensive incidence rates of dilated cardiomyopathy in first-degree relatives have never been reported before. Of note, the age at onset of dilated cardiomyopathy in individuals with a relative with dilated cardiomyopathy (median 44 years of age in our sample) is reassuringly similar to that noted in prior reports (mean ages of 37–40 years) [23]. Similar, the median age at onset of dilated cardiomyopathy of 49 years among the controls is comparable to that reported in sporadic cases before (mean age 48 years) [23].

4.2. Importance of conventional risk factors

A genetic susceptibility has been identified in approximately half of all familial dilated cardiomyopathy cases and in at least 20% of individuals with sporadic dilated cardiomyopathy, with the implicated genetic variants often being inherited in an autosomal dominant fashion [24,25]. This premise would suggest that up to half of all relatives of probands with dilated cardiomyopathy may potentially harbor an inherited, known disease-causing genetic variant in our study population. Yet, few relatives of probands developed dilated cardiomyopathy during follow-up, supporting the notion that the penetrance of dilated cardiomyopathy-related genetic variants is somewhat low. Of note, however, first-degree relatives to patients with dilated cardiomyopathy more often developed atrial fibrillation, hypertension, diabetes, and ischemic heart disease during follow-up than matched controls. These comorbidities could, in some cases, possibly represent a subclinical form of dilated cardiomyopathy. For instance, shared genetic loci and mutations are well-known for dilated cardiomyopathy and atrial fibrillation (such as laminin and TTN-truncating variants) [26,27], and have also been reported for dilated cardiomyopathy and hypertension (e.g., BAG-3, which is reportedly involved in both vascular homeostasis and blood pressure regulation) [28–30]. Of note, first-degree relatives with concomitant atrial fibrillation had an incidence rate of dilated cardiomyopathy exceeding 1 per 100 person-years, possibly reflecting a shared genetic substrate for the two conditions. These individuals likely warrant increased surveillance and focus on optimizing their medical therapy, as they appear to be at a particularly high risk of developing clinical dilated cardiomyopathy themselves. In addition to being risk markers, we hypothesize that ischemic heart disease and hypertension may act synergistically and jointly with genetic predisposition to increase the risk of developing both dilated cardiomyopathy and clinical heart failure. If this hypothesis is true, approximately 15% of all dilated cardiomyopathy cases in familial predisposed individuals could be prevented if hypertension was well-controlled (corresponding to the population attributable fractions associated with the presence of hypertension).

4.3. Strengths and limitations

The study was nationwide, complete, and based on a large sample of individuals with dilated cardiomyopathy. The diagnosis of dilated cardiomyopathy was based on real-life administrative registries and coded after physician adjudications and routine clinical assessments. The diagnosis has been validated (with additional validation undertaken in this study) and is accurate. Danish guidelines (as adapted from international consensus statements and guidelines) recommend that all first-degree family members to a proband with idiopathic dilated cardiomyopathy should be screened with electro- and echocardiography if the proband is below 50 (up to 60) years at dilated cardiomyopathy onset, or if there are at least 2 individuals with dilated cardiomyopathy in a family, which should encompass most first-degree relatives in this study [13,31,32]. The observed incidence rates in our control group were furthermore of similar magnitude to those reported in previous studies, supporting the validity of our estimates. Despite several strengths, major limitations included lack of granular information on several possible contributing factors to the etiology behind dilated cardiomyopathy, e.g. myocarditis, alcohol overuse, or obesity. Additionally, dilated

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cardiomyopathy may be classified as ischemic versus non-ischemic and although we performed several sensitivity analyses, including only the subgroup of probands without a known diagnosis of ischemic heart disease, residual confounding is possible, and a better classification of non-ischemic dilated cardiomyopathy could have been helpful. Further, the observational period was long and the extent and impact of changes in practice patterns for diagnosis and treatment of dilated cardiomyopathy that might occurred over the period is unknown. Finally, the lack of data on possible genetic variants involved in dilated cardiomyopathy must be acknowledged as a limitation.

4.4. Clinical implications

While the prevalence of genetic variation in dilated cardiomyopathy related genes can be assumed to be (more or less) constant over time, conventional risk factors and adverse lifestyle habits (including poor diet and physical inactivity) have been increasing over the past decades in young to middle-aged individuals [1]. In parallel hereto, reports have indicated that the incidence rates of dilated cardiomyopathy have increased in the same segment of the population [2,3,10]. These prior studies and our current observations underscore that although genetic variation is likely to be important, the presence of common risk factors (such as obesity, hypertension, diabetes, and ischemic heart disease) also increases the susceptibility for clinical dilated cardiomyopathy. Additional studies are warranted to evaluate whether the prevention and early treatment of standard risk factors can alter the risk of dilated cardiomyopathy and prevent development of clinical heart failure.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Schou has received lecture fees from Bohringer Ingelheim, AstraZeneca, and Novo Nordisk. Dr. Køber reports lecture fees from Novartis, BMS, and AstraZeneca. Dr. Torp-Pedersen has received study funding from Bayer and Novo Nordisk. All unrelated to the present work.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101065.

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