Risk of Cardiomyopathy in Younger Persons
With a Family History of Death from Cardiomyopathy:
A Nationwide Family Study in a Cohort of 3.9 Million Persons

Running title: Ranthe et al.; Premature death from CM and familial risk of CM

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Journal Subject Code: Etiology:[8] Epidemiology
Abstract:

**Background**—Recommendations for pre-symptomatic screening of relatives of cardiomyopathy patients are based on findings from tertiary centers. Cardiomyopathy inheritance patterns are fairly well understood, but how cardiomyopathy in younger persons (<50 years) aggregates in families at the population level is unclear. In a nationwide cohort, we examined the risk of cardiomyopathy by family history of premature death (<60 years) from cardiomyopathy.

**Methods and Results**—By linking Danish national register data, we constructed a cohort of 3.9 million persons born from 1950 to 2008. We ascertained family history of premature (<60yrs) death from cardiomyopathy or other conditions, and cohort members were followed from 1977 to 2008 for cardiomyopathy diagnosed at <50 years. We identified 3,890 cardiomyopathies in 89 million person-years of follow-up. Using Poisson regression, we estimated incidence rate ratios for cardiomyopathy by family history of premature death. Premature cardiomyopathy deaths in first- and second-degree relatives were associated with 29- and 6-fold increases in the rate of cardiomyopathy, respectively. If the first-degree relative died aged <35yrs, the rate of cardiomyopathy increased 100-fold; given ≥2 premature deaths in first-degree relatives, the rate increased more than 400-fold. In contrast, a family history of premature death from other cardiac or non-cardiac conditions increased the rate of cardiomyopathy 3-fold at most.

**Conclusions**—A family history of premature cardiomyopathy death was associated with an increase in risk of cardiomyopathy ranging from 6- to 400-fold, depending on age, kinship, gender and number of affected family members. Our general population-based results support recommendations for pre-symptomatic screening of relatives of cardiomyopathy patients.

**Key words:** cardiomyopathy, familial hypertrophic cardiomyopathy, family history, risk factor, cohort study, premature death
Introduction

Patients with cardiomyopathy may present with heart failure, arrhythmia or syncope; cardiomyopathies are also the leading causes of sudden cardiac death in persons <50 years of age. However, if cardiomyopathy is diagnosed early, potentially fatal complications can be prevented by means of medical treatment or device implantation.1,2 Cardiomyopathies in younger persons, including the hypertrophic, dilated, restrictive and arrhythmogenic right ventricular cardiomyopathies, show evidence of familial aggregation,3 with autosomal dominance the most frequent pattern of inheritance.4 Accordingly, the clinical workup of cardiomyopathy patients includes eliciting any history of cardiomyopathy in family members and screening relatives with unknown cardiomyopathy status.

North American and European guidelines for screening of the relatives of cardiomyopathy patients are predominantly based on the findings of studies conducted at tertiary referral centers.5,6 Not surprisingly, these studies are characterized by small sample sizes, an absence of “control” families, a focus on highly-selected cases and heavily-affected families, and self-reported family histories.7 While the study results undoubtedly reflect reality among families with the most severe cardiomyopathy phenotypes and the greatest burden of cardiomyopathy, their generalizability to the general population subject to current screening protocols is unclear and there is a consensus in the cardiology community that population-based studies of the familial aggregation of cardiomyopathy are needed.6–8

Using the Danish population as our cohort, we examined the degree to which cardiomyopathy in younger persons (<50 years) aggregates in families at the population level, by comparing the rate of cardiomyopathy in younger persons with a relative who died prematurely (<60 years) from cardiomyopathy (a very severe cardiomyopathy phenotype) with the rate of
cardiomyopathy in younger persons without such a family history. We assessed the impact of the number, type (first- vs. second-degree), sex and age of relatives dying from cardiomyopathy, along with cohort member age, on risk of cardiomyopathy at <50 years, with the goal of providing an epidemiologic basis for the current recommendations for family screening in cardiomyopathy.

Methods

Data sources

Since 1968, the Danish Civil Registration System has registered demographic, vital status, and kinship information on all persons residing in Denmark, aided by the unique personal identification number (PIN) assigned to each Danish resident. The PIN permits accurate linkage of individual-level information from all of Denmark’s nationwide registers.9 Using the kinship information in the Civil Registration System, the Department of Epidemiology Research at Statens Serum Institut has developed the Danish Familial Relations Database, a unique database that can identify first-degree relatives (parents, children and siblings) and half-siblings (second-degree relatives) resident in Denmark for most persons born in 1950 or later. In addition, other second-degree relatives (grandparents, grandchildren, aunts/uncles, nieces/nephews) can also be identified for almost 90% of individuals born in 1985 or later. The Danish National Hospital Discharge Register contains information from all Danish hospitals on inpatient diagnoses assigned since 1977 and outpatient diagnoses from 1995 onward.10 Diagnoses are registered using International Classification of Disease (ICD) codes, with ICD-8 codes used from 1977 to 1993 and ICD-10 codes used from 1994 onward. The Causes of Death Register, which began in 1970, contains death certificate information, including contributing and underlying causes of
death, main diseases and recent procedures and medication.\textsuperscript{11,12}

\textbf{Study cohort, identification of relatives and assessment of premature deaths among relatives}

The study cohort included all residents of Denmark who 1) were born in 1950-1977 and were still alive on January 1, 1978, or who were born thereafter, and 2) had at least one identifiable relative in the Danish Family Relations Database. For each cohort member, we used the Danish Family Relations Database to identify first- and second-degree relatives. We then identified premature deaths (death occurring before age 60 years) in relatives using the Causes of Death Register.

Premature cardiac deaths were defined as deaths < 60 years with death certificate causes of death that included ICD-8 codes 390.00-429.99 or ICD-10 codes I00-I51. Premature deaths with none of these cardiac codes on the death certificate were classified as premature non-cardiac deaths. As we have done previously, we excluded deaths that might possibly have been misclassified cardiac deaths (deaths due to stroke, cerebral hemorrhage, asthma, epilepsy, solo accidents and unexplained causes) from both the cardiac and non-cardiac categories.\textsuperscript{12} We also examined two specific sub-groups of cardiac death: premature deaths from ischemic heart disease (ICD-8 codes 410-414.99 and ICD-10 codes I20-I25.9) and premature deaths from cardiomyopathy (ICD-8 code 425.99 and ICD-10 codes I42-I43.8). Since ischemic heart disease can produce secondary cardiomyopathy, persons with both ischemic heart disease and cardiomyopathy diagnoses on the death certificate were classified as having died of ischemic heart disease. A death was presumed to be due to cardiomyopathy only in the absence of an ischemic heart disease diagnosis on the death certificate, resulting in a very conservative definition of premature deaths from cardiomyopathy.
Assignment of exposure status

Family history of premature death was considered as a time-dependent variable. A cohort member was classified as exposed from the date of death of the first relative (if any) to die from the type of premature death in question (non-cardiac, any cardiac, ischemic, cardiomyopathy). If the premature death occurred before birth of the cohort member, the cohort member was considered exposed from birth. If there were no premature deaths in a cohort member’s family, all follow-up time was classified as unexposed.

Outcome

Persons diagnosed with cardiomyopathy during follow-up (ICD-8 code 425.99; ICD-10 codes I42-I43.8 – see Table 1 for a description of the cardiomyopathy subtypes covered by these ICD-10 codes) were identified using the National Hospital Discharge Register. Since ventricular arrhythmia is a well-known and serious complication of cardiomyopathy1, as well as a potential first manifestation of the disease, we also identified cohort members registered in the Hospital Discharge Register with ventricular arrhythmia (ICD-8 codes 427.91 and 427.97; ICD-10 codes I46, I47.0, I47.2 and I49.0.

Statistical analysis

Data were treated as time-to-event data and analyzed using survival analysis. Follow-up started on January 1, 1978 or at birth, whichever came later, and continued until the first of the following events: 1) cardiomyopathy or ventricular arrhythmia (separate analyses); 2) 50th birthday; 3) death; 4) emigration; 5) designated “missing” in the CRS; or 6) December 31, 2008 (end of follow-up). Events and observation time were aggregated according to covariates and analyzed using log-linear Poisson regression with logarithm of the aggregated observation times as offset (assuming constant rates within combination of the covariates). Thus, using log-linear
Poisson regression, we estimated incidence rate ratios (IRRs) comparing the rate of for cardiomyopathy among those with a relative who died before age 60 years compared with those with no such relatives; we estimated separate IRRs for non-cardiac premature deaths and the three types of premature cardiac death (any cardiac death, death due to ischemic heart disease, and death due to cardiomyopathy). We also examined associations with premature death by kinship degree (first- or second-degree), number of affected relatives (1 or ≥2), relative’s age at death, cohort member attained age, and relative type (parent, sibling, grandparent, half-sibling, uncle/aunt). Finally, we estimated IRRs for associations between premature cardiomyopathy deaths in first- and second-degree relatives and rates of ventricular arrhythmia.

In relative-specific analyses, we compared only individuals having the same kind of relatives to reduce any bias that might result from incomplete identification of family members from older birth cohorts (due to the structure of the Civil Registration System and the Danish Family Relations Database), as well as to adjust the IRR for any possible effect produced by the simple fact of having the specific type of relative in question. All IRRs were adjusted for attained age (1-year groups), calendar period (4-year periods from 1977-2006 and 2007-2008) and sex.

Tests were based on Wald statistics and analyses were performed using proc genmod in the SAS software.

Ethics

The Department of Epidemiologic Research at Statens Serum Institut has approval from the Danish National Board of Health and the Danish Data Protection Agency to conduct register-based epidemiologic studies. As the study was entirely register-based, approval from the local ethics committee was not required.
Results

Our cohort included 3,985,301 persons followed for 89,272,960 person-years. Of these, 34,362 had at least one relative who died prematurely of cardiac causes. Of those with a family history of premature cardiac death, 27,162 had a family history of premature death due to ischemic heart disease, while 778 had one or more premature cardiomyopathy deaths in the family. In contrast, 223,349 persons had a family history of premature death due to non-cardiac causes.

During follow-up, 3,890 persons were diagnosed with cardiomyopathy; the median age at diagnosis was 38 years. Table 2 shows the distribution of sex and age at diagnosis for those registered with cardiomyopathy during the follow-up period.

Associations between family history of premature death and rate of cardiomyopathy (Table 3)

Persons <50 years of age with a first-degree relative who died prematurely of any cardiac cause had a rate of cardiomyopathy that was almost 3 times higher than that in persons with no such family history, while persons with a history of premature cardiac death in a second-degree relative had a 58% increase in cardiomyopathy rate. Persons who specifically had a history of premature cardiomyopathy death in a first-degree relative were 30 times as likely as persons with no premature cardiomyopathy deaths among first-degree relatives to be diagnosed with cardiomyopathy before 50 years of age. Even a history of premature cardiomyopathy death in a second-degree relative was associated with a 6-fold increase in the rate of cardiomyopathy. In comparison, premature deaths in first-degree relatives due to ischemic heart disease were associated with a 2-fold increase in the rate of cardiomyopathy. Premature non-cardiac deaths in first-degree relatives were only associated with a 24% increase in the rate of cardiomyopathy.

Associations between family history of premature death from cardiomyopathy and rate of cardiomyopathy, by sex, age and relative’s age at death
Among men, the IRRs for cardiomyopathy before age 50 years by history of premature death from cardiomyopathy in first- and second-degree relatives were 25.0 (95% confidence interval [CI] 17.6-35.4) and 7.23 (95% CI 3.00-17.4), respectively. Among women, the IRR for cardiomyopathy by history of premature death from cardiomyopathy in first-degree relatives was 43.4 (95% CI 28.7-65.6; p-value for homogeneity of estimates for males and females: 0.05); there was only one woman with both an affected second-degree relative and a cardiomyopathy diagnosis, making it impossible to produce a useful IRR estimate for deaths in second-degree relatives.

Since congenital heart disease might be misclassified as cardiomyopathy, we also conducted a sub-analysis restricted to cohort members ≥10 years of age. In this analysis, IRRs for cardiomyopathy before age 50 years were 27.8 (95% CI 20.9-37.0) for a history of premature death from cardiomyopathy in a first-degree relative and 16.0 (95% CI 7.13-35.8) for those with such a history in a second-degree relative. Table 4 shows the effect of first-degree relative age at death and cohort member attained age on the IRR for cardiomyopathy. Attained age <35 years and age at relative death <35 years were both particularly strongly associated with cardiomyopathy rate (Table 4). If a first-degree relative died from cardiomyopathy at <35 years of age, the rate of cardiomyopathy increased up to 100-fold, but even cardiomyopathy deaths in older relatives were associated with dramatic increases in cardiomyopathy rates (Table 4).

**Associations between number of premature cardiomyopathy deaths in the family and rate of cardiomyopathy**

The strength of the association depended on the number of relatives who died prematurely from cardiomyopathy (Table 5). Having ≥2 relatives who died prematurely from cardiomyopathy increased the IRRs dramatically compared with having only one relative who died, particularly
for first-degree relatives.

**Associations between premature death from cardiomyopathy in specific relatives and rate of cardiomyopathy**

IRRs for cardiomyopathy differed little by affected relative type. IRRs for premature death from cardiomyopathy in parents and siblings were 26.7 (95% CI 19.7-36.0) and 29.7 (17.4-50.6), respectively. IRRs for different types of second-degree relatives differed somewhat more, but confidence intervals were wide (reflecting small numbers of exposed persons diagnosed with cardiomyopathy) and overlapping. IRRs for premature deaths from cardiomyopathy in half-siblings, aunts/uncles and grandparents were 27.7 (3.84-195), 8.09 (2.57-25.4) and 4.26 (1.35-13.4), respectively.

**Association between premature cardiomyopathy deaths in relatives and rate of ventricular arrhythmia**

Persons with a family history of premature death from cardiomyopathy in a first-degree relative had a 7-fold increase in the rate of ventricular arrhythmia (IRR 7.21, 95% CI 4.60-11.3) compared with persons without such a family history. The corresponding estimate for those with premature death in a second-degree relative was 3.82 (95% 1.43-10.2).

**Discussion**

This is the first large, population-based study to examine the risk of cardiomyopathy before age 50 years associated with a family history of premature death from cardiomyopathy. Any premature cardiac death in a first-degree relative was associated with an almost 3-fold increase in the rate of cardiomyopathy before 50 years of age, compared with the rate in persons without premature cardiac deaths among first-degree relatives; premature cardiac deaths in second-degree relatives
were also associated with modestly increased rates of cardiomyopathy. If a first-degree relative
died specifically of cardiomyopathy, the rate of cardiomyopathy before age 50 years increased by a
markedly 30-fold, and even cardiomyopathy deaths in second-degree relatives were associated
with a 6-fold increase in the rate of cardiomyopathy. In contrast, ischemic heart disease deaths in
first-degree relatives were associated with only a 2-fold increase in cardiomyopathy rate and non-
cardiac deaths increased the rate of cardiomyopathy very little (24%).

The association between a history of premature cardiomyopathy death in first-degree
relatives and cardiomyopathy rates appeared to be stronger for women than men. The rate of
cardiomyopathy increased even more if the cardiomyopathy death in the first-degree relative
occurred before 35 years of age (>100-fold increase in rate), and if ≥2 first-degree relatives had
died from cardiomyopathy, the rate of cardiomyopathy increased more than 400-fold.
Cardiomyopathy deaths in second-degree relatives were also associated with increases in
cardiomyopathy rates, although to a lesser extent (5-to 65-fold increases). We also found
significant increases in ventricular arrhythmia rates in those with a family history of premature
defeat from cardiomyopathy among first- or second-degree relatives.

Our results show that the strong familial aggregation of cardiomyopathy demonstrated in
case studies of selected families identified by tertiary referral institutions, also holds in the
general population; associations between a family history of premature death and risk of
cardiomyopathy were most dramatic for familial cardiomyopathy deaths and were much weaker
for ischemic and other cardiac deaths. Deaths in first-degree relatives were much more strongly
associated with cardiomyopathy risk than deaths in second-degree relatives (although risks
associated with these deaths were by no means inconsiderable), consistent with the proportion of
shared genes among first- and second-degree relatives and the genetic inheritance of an
autosomal dominant trait with variable penetrance.

**Clinical Implications**

The observed increases in risk of clinically diagnosed cardiomyopathy (ranging from 6- to 400-fold) in persons with a family history of premature cardiomyopathy death strongly support the present recommendations for pre-symptomatic screening in families with cardiomyopathy. Ventricular arrhythmia is a life-threatening complication of cardiomyopathy and may be the first symptom of disease. The observed 3- to 7-fold increased risk of ventricular tachycardia in persons with a family history of premature death from cardiomyopathy further underlines the importance of pre-symptomatic screening and early intervention.

Our ability to grade the risk depending on age at clinical manifestations in the proband and kinship, gender and number of affected family members may allow for more detailed recommendations regarding when to initiate screening and risk assessment in individual relatives.

A vast number of cardiomyopathy-causing mutations have been identified to date\textsuperscript{13,14}, making genetic testing a useful tool for identifying relatives at risk of developing cardiomyopathy due to cardiomyopathy in a relative; if a disease-causing mutation can be identified in a family, family members who are not carriers can be excluded from further follow-up. However, in up to 50\% of families screened, no disease-causing mutation can be identified in the proband,\textsuperscript{8,14} and no genetic differentiation between at-risk relatives and those who are risk-free is possible. In these families, all relatives need clinical follow-up. Furthermore, genetic testing may be a challenging and expensive process in some settings.

Our study identified elements of family history that could be useful for grading risk in persons with a family history of cardiomyopathy death. The overwhelming associations between...
very early (<35 years of age) cardiomyopathy death in a first-degree relative and risk of cardiomyopathy in all age groups suggest that anyone with this family history has an exceptionally strong predisposition to a very serious cardiomyopathy phenotype. Furthermore, our finding that cardiomyopathy risk was “dose-dependent”, increasing with increasing number of affected relatives for both first- and second-degree relatives, indicates that persons with more than one cardiomyopathy death in the family, even if these deaths are “only” in second-degree relatives, are at very high risk of cardiomyopathy.

Our study identified approximately 4,000 patients registered with cardiomyopathy, among nearly 4 million persons. Assuming this number corresponds to an overall cardiomyopathy prevalence of 1:1000, it is interesting to compare this number to the generally reported prevalences for the most frequent cardiomyopathies: hypertrophic cardiomyopathy, 1:500\(^6\), dilated cardiomyopathy, 1:2,500\(^{15}\); and arrhythmogenic right ventricular cardiomyopathy, 1:2,000-1:5,000\(^{16}\) for a combined prevalence of 2:1,000-3:1,000. Considering that clinically confirmed hypertrophic cardiomyopathy is often reported considerably lower than 1:500, due to cardiomyopathies being subclinical or under- or misdiagnosed\(^{17,18}\), our observed cardiomyopathy prevalence and the reported prevalences seem to be in reasonable accordance. The remaining discrepancy may reflect that pre-symptomatic family screening in Denmark has not been completely effective.

**Potential Limitations and Strengths**

Despite its enormous size and use of Danish register data, our study had some potential limitations. We were forced to consider all cardiomyopathies as a single disease entity due to a lack of clinical information (e.g. septum thickness, ejection fraction, genotype) and to the very limited level of detail in registered diagnosis codes, particularly before 1994 when the ICD-8
system, which had only a single cardiomyopathy code, was used. Even after 1994, when the ICD-10 system offered the potential for more detailed diagnoses, a considerable proportion (39%) of cardiomyopathy diagnoses in the Hospital Discharge Register were non-specific (“other” or “unspecified” cardiomyopathy) (Table 1). On the other hand, recent studies have shown that the same genetic mutations can cause both dilated and hypertrophic cardiomyopathies, and even that cardiomyopathy in an individual can evolve over time from one sub-type to another, such that considering the cardiomyopathies as a combined group seems justified.19

Cardiomyopathies can be divided into primary cardiomyopathies and cardiomyopathies arising secondary to another condition, with the former clearly of greatest interest in a familial aggregation study such as ours. However, cardiomyopathy subtypes were not available in ICD-8 and a large proportion of cardiomyopathies registered using ICD-10 codes were not subtyped either. We assumed, however, that the bulk of the “unspecified” cardiomyopathies were primary cardiomyopathies, an assumption supported by data from the Hospital Discharge Register showing that from 1994 to 2010, <12% of cardiomyopathies in persons <50 years of age were secondary to another condition (endomyocardial (eosinophilic) cardiomyopathy, endocardial fibroelastosis, alcoholic cardiomyopathy, drug-induced cardiomyopathy, and cardiomyopathy secondary to other diseases). Table 1. Since these secondary cardiomyopathies are unlikely to be familial, if their inclusion in our study had any effect, it would have been to weaken the magnitude of our familial aggregation estimates.

In the very young, congenital heart disease may initially be misdiagnosed as cardiomyopathy. However, analyses excluding persons aged <10 years produced results similar to our main analyses and in fact, the association between a history of cardiomyopathy death in
second-degree relatives and rate of cardiomyopathy appeared even stronger in the restricted analysis.

A not-insubstantial number of cardiomyopathies were almost certainly misclassified as heart failure, particularly early in the study period and before the advent of echocardiography, but also later on, reflecting variations in diagnostic practice at different hospitals. Once again, however, if anything, such misclassification would have weakened the true magnitude of the familial aggregation of cardiomyopathy in our study.

Data on behavioral risk factors for cardiomyopathy, such as alcohol consumption, are unavailable on a nationwide level, and secondary cardiomyopathies could therefore not be excluded. However, the number of cardiomyopathies identified during follow-up that were secondary to ischemic heart disease, alcohol or drug use is likely to have been small relative to the number of primary, familial cardiomyopathies, particularly in the younger age groups that were the focus of our study. Consequently, the lack of behavioral risk factor information is unlikely to have been a problem.

Surveillance bias might have affected our results if relatives of a premature cardiomyopathy death victim were more likely to seek medical attention after the death and be diagnosed with cardiomyopathy than persons without such a death in the family. However, the systematic family screening approach to inherited cardiovascular disease only emerged in Denmark late part in the study period (after 2006\textsuperscript{20}) and thus it seems unlikely that our findings of very high relative risks reflects targeted family workups in tertiary centers at selected hospitals. If surveillance bias was a major problem, we might also have expected to see equally strong associations between other types of premature cardiac deaths in relatives and rates of cardiomyopathy. However, IRRs for associations with cardiac deaths (overall) and ischemic
heart disease deaths were not greater than 3, whereas estimates for cardiomyopathy deaths were generally at least ten times larger, suggesting that surveillance bias did not have a major influence on our results.

Major strengths of our study included the large cohort size, our ability to assess family history without contacting study subjects (thus avoiding recall bias), and comparison of exposed and unexposed families (in contrast to typical hospital-based studies). Only clinically diagnosed cases were included. Furthermore, we included associations with premature non-cardiac deaths and other types of cardiac deaths for comparison. Finally, our use of an entire country as our cohort suggests that our findings are likely to be broadly generalizable.

Conclusion

In this nationwide study, a family history of premature cardiomyopathy death was associated with an increase in risk of clinically diagnosed cardiomyopathy ranging from 6- to 400-fold, depending on age at clinical presentation, kinship, gender, age and number of affected family members. The risk of serious complications in the relatives was illustrated by the finding of their 3- to 7-fold increase in risk of ventricular arrhythmia. Our general population-based results strongly support the recommendations for pre-symptomatic screening of relatives of patients with cardiomyopathy in order to be able to reduce morbidity and mortality through early intervention.

Acknowledgments: Mattis F. Ranthe and co-authors at Statens Serum Institut, Department of Epidemiology Research had full access to all of the data in the study. Mattis F. Ranthe takes full responsibility for the integrity of the data and the accuracy of the data analysis. This study was designed and conducted at Department of Epidemiology Research, Statens Serum Institut by the collective group of authors, the study was lead by Dr. Ranthe in the period 2012-2013. Dr
Ranthe was employed at the Department from 2010-2013. At time of this submission, however Dr. Ranthe is an employee of Novo Nordisk A/S. Novo Nordisk A/S had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

**Funding Sources:** This work was supported by the Danish Heart Foundation, grant nos. 10-04-R78-A2799-22615 and 06-4-B571-A1059-22307 and the Lundbeck Foundation, grant no. 287/06. The Danish Heart Foundation and the Lundbeck Foundation had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

**Conflict of Interest Disclosures:** MF Ranthe was employed by Statens Serum Institut at the time this study was conducted. However, at the time of submission, he was employed by Novo Nordisk A/S, Søborg, Denmark. Novo Nordisk A/S played no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. None of the remaining authors has any relationship with industry to declare.

**References:**


15. Mcnally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated


Table 1. Subtype distribution for cardiomyopathies in the Danish population diagnosed at less than 50 years of age, 1994-2010

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Description</th>
<th>N</th>
<th>%</th>
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<tr>
<td>I42</td>
<td>Cardiomyopathy</td>
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<td>I42.0</td>
<td>Dilated cardiomyopathy</td>
<td>1,532</td>
<td>32.4</td>
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<tr>
<td>I42.1</td>
<td>Obstructive hypertrophic cardiomyopathy</td>
<td>354</td>
<td>7.5</td>
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<tr>
<td>I42.1A</td>
<td>Hypertrophic subaortic stenosis</td>
<td>2</td>
<td>0.04</td>
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<tr>
<td>I42.2</td>
<td>Other hypertrophic cardiomyopathy</td>
<td>379</td>
<td>8.0</td>
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<td>I42.3</td>
<td>Endomyocardial (eosinophilic) disease</td>
<td>7</td>
<td>0.15</td>
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<tr>
<td>I42.3B</td>
<td>Löfflers endocarditis</td>
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<td>0.02</td>
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<td>I42.4</td>
<td>Endocardial fibroelastosis</td>
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<td>Congenital cardiomyopathy</td>
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<td>I42.5</td>
<td>Other restrictive cardiomyopathy</td>
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<td>0.66</td>
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<td>I42.6</td>
<td>Alcoholic cardiomyopathy</td>
<td>250</td>
<td>5.3</td>
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<td>I42.7</td>
<td>Cardiomyopathy due to drugs and other external agents</td>
<td>57</td>
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<td>I42.8</td>
<td>Other cardiomyopathies</td>
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<td>I42.8A</td>
<td>Arrhythmogenic right ventricular dysplasia (ARVD)</td>
<td>41</td>
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<td>I42.8B</td>
<td>Takotsubo cardiomyopathy</td>
<td>5</td>
<td>0.11</td>
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<td>I42.9</td>
<td>Cardiomyopathy, unspecified</td>
<td>1,624</td>
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<td>I43</td>
<td>Cardiomyopathy in diseases classified elsewhere</td>
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4,723 100
**Table 2.** Cohort Characteristics, Persons with Cardiomyopathy and follow-up by age, sex, and family history. Characteristics on 3,890 persons with cardiomyopathy in a cohort of 3,985,301 persons born in 1950 or later. The cohort was followed for 89,272,960 person-years from 1977 to 2008 in Denmark.

<table>
<thead>
<tr>
<th>Age at Cardiomyopathy</th>
<th>Persons With CM (n=3,890)</th>
<th>Duration of follow up, person years x 10³</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9 years</td>
<td>413 (10.6%)</td>
<td>19,942</td>
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<tr>
<td>10-19 years</td>
<td>261 (6.7%)</td>
<td>20,839</td>
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<tr>
<td>20-29 years</td>
<td>497 (12.8%)</td>
<td>21,620</td>
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<td>30-39 years</td>
<td>1,006 (25.9%)</td>
<td>17,109</td>
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<tr>
<td>40-49 years</td>
<td>1,713 (44.0%)</td>
<td>9,760</td>
</tr>
</tbody>
</table>

Sex
- Female 1,192 (31%) 43,617
- Male 2,698 (69%) 45,655

Number and proportion with identifiable relatives*
- First-degree relative† 3,382 (87%) 82,348
- Second-degree relative‡ 938 (24%) 31,330

Abbreviations: CM, Cardiomyopathy;
* Cohort members could contribute more than 1 type relative to the analyses; numbers add up to more than 3,890 persons (100%).
† First-degree: parents, children and siblings.
‡ Second-degree: grandparents, grandchildren, half-siblings, uncles, aunts, nieces and nephews.
Table 3. Incidence Rate Ratios of Cardiomyopathy by Family History of Premature Death (<60 years). Incidence rate ratios with 95% confidence intervals for cardiomyopathy in persons with one or more first- or second-degree relatives who died before age 60 years compared to persons with similar relatives who did not die before age 60 years, follow-up from 1977 to 2008.

<table>
<thead>
<tr>
<th>Family history:</th>
<th>Number of persons with CM and the specified family history</th>
<th>Duration of follow up, person years x 10&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Incidence rate ratios* with 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature deaths from cardiomyopathy in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative</td>
<td>55</td>
<td>46</td>
<td>30.39 (23.28-39.69)</td>
</tr>
<tr>
<td>Any second-degree relative</td>
<td>6</td>
<td>33</td>
<td>6.05 (2.71-13.52)</td>
</tr>
<tr>
<td>Premature cardiac deaths in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative</td>
<td>275</td>
<td>1.968</td>
<td>2.87 (2.54-3.26)</td>
</tr>
<tr>
<td>Any second-degree relative</td>
<td>64</td>
<td>1.653</td>
<td>1.58 (1.23-2.04)</td>
</tr>
<tr>
<td>Premature deaths from ischemic heart disease in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative</td>
<td>164</td>
<td>1.589</td>
<td>1.98 (1.69-2.32)</td>
</tr>
<tr>
<td>Any second-degree relative</td>
<td>50</td>
<td>1.381</td>
<td>1.49 (1.12-1.98)</td>
</tr>
<tr>
<td>Premature non-cardiac deaths in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative</td>
<td>436</td>
<td>8.216</td>
<td>1.24 (1.12-1.38)</td>
</tr>
<tr>
<td>Any second-degree relative</td>
<td>152</td>
<td>5.925</td>
<td>0.96 (0.80-1.14)</td>
</tr>
</tbody>
</table>

Abbreviations: CM, Cardiomyopathy; CI, confidence interval
*Incidence rate ratios are adjusted for age, sex and calendar period
For definitions of first- and second-degree relatives, see Table 1.
Table 4. Incidence Rate Ratios of Cardiomyopathy by Age of Relative at Death and Attained Age Cohort Member. Incidence rate ratios with 95% confidence intervals for cardiomyopathy in persons with one or two or more first- or second-degree relatives who died before age 60 years from cardiomyopathy compared to persons with similar relatives who did not die before age 60 years, follow-up from 1977 to 2008.

<table>
<thead>
<tr>
<th>Family history of death from cardiomyopathy in a first degree relative</th>
<th>Incidence rate ratios* with 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- aged less than 35 years at time of death</td>
<td></td>
</tr>
<tr>
<td>Cohort members attained age</td>
<td>106 (64.4-175)</td>
</tr>
<tr>
<td>&lt;35y</td>
<td>111 (64.3-192)</td>
</tr>
<tr>
<td>35y or more</td>
<td>54.2 (13.52-218)</td>
</tr>
<tr>
<td>- aged between 35 and 60 years at time of death</td>
<td>22.3 (16.3-30.4)</td>
</tr>
<tr>
<td>Cohort members attained age</td>
<td>33.2 (22.6-48.7)</td>
</tr>
<tr>
<td>&lt;35y</td>
<td>13.1 (7.58-22.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CM, Cardiomyopathy; CI, confidence interval

*Incidence rate ratios are adjusted for age, sex and calendar period

Table 5. Incidence Rate Ratios of Cardiomyopathy by Number of Relatives and Degree of Kinship. Incidence rate ratios with 95% confidence intervals for cardiomyopathy in persons with one or two or more first- or second-degree relatives who died before age 60 years from cardiomyopathy compared to persons with similar relatives who did not die before age 60 years, follow-up from 1977 to 2008.

<table>
<thead>
<tr>
<th>Family history of death from cardiomyopathy before age 60 years</th>
<th>Number of persons with CM and the specified family history</th>
<th>Duration of follow up, person years x 10^5</th>
<th>Incidence rate ratios* with 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relatives(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>52</td>
<td>45</td>
<td>29.11 (22.13-38.31)</td>
</tr>
<tr>
<td>Two or more</td>
<td>3</td>
<td>0.2</td>
<td>455.3 (146.7-1443)</td>
</tr>
<tr>
<td>Second-degree relative(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>5</td>
<td>0.2</td>
<td>5.16 (2.14-12.43)</td>
</tr>
<tr>
<td>Two or more</td>
<td>1</td>
<td>1.7</td>
<td>65.95 (9.28-468.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CM, Cardiomyopathy; CI, confidence interval

*Incidence rate ratios are adjusted for age, sex and calendar period

For definitions of first- and second-degree relatives, see Table 1.
Risk of Cardiomyopathy in Younger Persons With a Family History of Death from Cardiomyopathy: A Nationwide Family Study in a Cohort of 3.9 Million Persons
Mattis F. Ranthe, Lisbeth Carstensen, Nina Øyen, Morten K. Jensen, Anna Axelsson, Jan Wohlfahrt, Mads Melbye, Henning Bundgaard and Heather A. Boyd

Circulation. published online August 14, 2015;

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