Familial clustering of myocardial infarction in first-degree relatives: a nationwide study

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Aims
Family history is an established risk factor for myocardial infarction (MI), but it is not clear how this risk changes with number and gender of first-degree relatives with MI. We used the entire Danish population to examine the importance of MI in siblings and parents.

Methods and results
This study is a retrospective nationwide register-based cohort study including registered relatives to all Danish citizens diagnosed with MI in the period 1978–2010. In the entire Danish population we identified siblings to 7552 patients with a first-time MI. The rate ratios (RR) calculated by Poisson models showed an RR of 4.30 (95% confidence interval 3.53–5.23) for siblings of a patient with MI. Children of parents with MI also showed high risk: for children of a maternal case RR 2.40 (2.20–2.60), and of a paternal case RR 1.98 (1.98–2.09), respectively; P value for gender interaction, 0.0001. A paternal case with MI at an age < 50 years was associated with an RR of 3.30 (2.92–3.72) while a case ≥50 years was associated with a risk of 1.83 (1.73–1.93). For maternal cases below and above 50 years of age the risks were 3.23 (2.56–4.10) and 2.31 (2.11–2.52), respectively.

Conclusion
First-degree relatives of a patient with myocardial infarction themselves have a substantial higher risk of myocardial infarction. The risk is particularly elevated when the MI case is the mother or a sibling, and when the MI case has the infarction before the age of 50 years.

Keywords
Familial clustering • Myocardial infarction • First-degree relatives

Introduction
Ischaemic heart disease is a leading cause of death in the western world. Several previous epidemiological studies have shown that a family history of cardiovascular disease (CVD) could be a risk factor for CVD in first-degree relatives. Other studies have demonstrated a trend towards familial clustering of myocardial infarction (MI) in first-degree relatives, independent of age, sex, and history of smoking, but subjects with fatal MI were excluded from these analyses. At least one previous study thoroughly investigated whether this familial clustering could be explained by the sharing of established risk factors, such as overweight, lipids, and blood pressure, but this was not the case. It has also been suggested that especially early-onset MI exhibits familial clustering.

Despite these previous studies, literature on the subject is scarce. Such previous studies were mostly small and obtained family history through questionnaires—a method prone to bias. Therefore, large studies with complete information on family history are warranted to firmly establish the risk of family members of an MI patient.

Methods
Since 1954, there is close to complete registration of parents to individuals born in Denmark as well as complete data on hospital diagnosis and cause of death. We used these data to examine the risk of MI in first-degree relatives of individuals with a history of MI.

Data were obtained from four large Danish registries, The Danish Civil Registration System, The Danish National Patient registry, the Cause of Death Registry, and the Danish National Prescription Registry. Every inhabitant in Denmark receives a unique and permanent civil registration number at birth or immigration that enables linkage...
between nationwide registers on the individual level. This civil registration number is connected to the Danish National Patient Registry that contains information on hospital admission with diagnoses coded according to the International Classification of Diseases (ICD) and has recorded admissions since 1977 and from this year till 1994 the ICD-8 was used and from 1994 and up until now the ICD-10 was used. Information on parents, children, and siblings is almost completely registered since 1954 through the Danish Civil Registration System that additionally contains information on gender and date of births. The date of death and causes of death, which is classified according to the ICD, which is also connected to the person’s civil registration number, was obtained from the Cause of Death Register.

In the Danish National Patient Registry we identified patients with the diagnosis of MI; we only included first-time diagnosis of MI with ICD-10 codes I21 and I22, and for patients diagnosed before 1996 we included the ICD-8 diagnose I410, and included both fatal and non-fatal events. Fatal events were collected either from hospital diagnoses or from the Cause of Death Register. The diagnosis of MI obtained from the Danish National Registry of Patients has been validated with acceptable/good sensitivity, specificity, and positive predictive values.7

Comorbidities were also obtained from the Danish National Patient Registry through their ICD-10 label. We chose the diagnosis of peripheral vascular disease (I70, I74, or I443), cerebrovascular disease (I60, I69, 430, or 438), renal disease (N03, N04, N17, N18, N19, R34, I12, I13, T858, T859, Z992, S82, S83, S84, S85, S86, or S88), and chronic obstructive lung disease (J42, J44, or 490, 491, 492). Further we obtained information on claimed prescriptions of relevant cardiovascular medication through the Danish Registry of Medicinal Product Statistics (the National Prescription Registry) identified through their international Anatomical Therapeutical Chemical classification system.9 We included the following medications in the multivariate analysis; glucose-lowering medication (A10) as a proxy for diabetes, statins (C10) as a proxy for hypercholesterolaemia, and low-dose aspirin (B01AC06) as a proxy for a recognized elevated risk of cardiovascular disease. Individuals with hypertension were also identified according to prescription claims. In accordance with the previous work,10 an individual who claimed at least two of the following anti-hypertensive drugs was considered to have hypertension: alfa-adrenergic drugs (C02A, C02B, and C02C), vasodilators (C02DB, C02DD, C02DG, C04, and C05), beta-blockers (C07), calcium channel blockers (C07F, C09BB, C09DB, and C08), renin–angiotensin system inhibitor (C09) and non-loop diuretics (C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C02DA, C09BA, C09DA, and C09XAS2). This definition of hypertension has previously been validated in a Danish cohort study.10

The first sibling in a sibship (group of siblings with the same mother), to be diagnosed with MI, would be named the index case, and similar with analysis on parents and children, the parent is the index case. After identification of the index case (the first one to experience MI), the siblings/children to this index case start their risk-time on the date their index case experience MI, and the index case will not participate in the further analysis. Identification of first-degree family members was obtained through the Danish Civil Registration system. Adopted children were excluded from the analysis.

**Statistical analysis**

The incidence of MI was modelled as a function of age (5-year intervals), sex, and calendar time (5-year intervals).

In a first step of the analysis, we determined the incidence of MI in the full population using Poisson regression.11 In a second step, the population results were used as fixed reference levels. Subpopulations were constructed to assess if history of MI in the family was associated with elevated MI incidence. For sibships, the first sibling (the index case) to have an event defined that history of MI was present in the family from the date of the first sibling’s MI. The rest of the siblings were included in the subpopulation and their risk time started at the date of the event of the first sibling and stopped at either death or at an event (i.e. fatal or non-fatal MI). If none of these endpoints were fulfilled the risk time was stopped (censored) on 31 December 2010. For each case in the subpopulation the expected number of MI events was calculated based on the reference rates for the full population and used as individual offset in Poisson regression. The resulting rate ratios (RR) were reported with 95% confidence limits that were based on robust standard errors taking into account the clustered data structure within families. Analogously, separate analyses were performed to assess the risks of having an MI if there was a history of MI for the mother or the father.

Comorbidities were also modelled as a function of age, sex, and calendar time for both the background population and the case populations; thus, every individual in the subpopulations had their prescription claims, and date of first prescription claim noted for the previously listed medication, as well as their diagnoses and diagnoses date for the previously listed diseases. By using this method the comorbidities (through either diagnosis or prescription claims) are specific for every person and at every age, sex, and calendar time interval and their comorbidities are included as time varying covariates at time of first claimed prescription or diagnosis. All calculations were performed in SAS, version 9.2 (SAS institute, Cary, NC, USA).

**Results**

In a total population of 8 890 990 consecutive Danish citizens, a total of 333 344 subjects had a first-time MI between 1978 and 2010. We identified 53 983 offspring of 29 188 maternal index cases and 194 507 offspring of 96 650 paternal index cases. In the total population, 3 975 949 Danish citizens were born after 1954, a total of 7552 had a first-time diagnosis of MI, 1709 of these had no siblings, for the remaining 5843 index cases we were able to identify 11 123 siblings. Figure 1 displays a flowchart of the study design and inclusion/exclusion criteria. Table 1 shows baseline characteristics of index cases and Table 2 shows the baseline characteristics of the cases. Baseline for the index cases was defined as the date of MI of the index case. Baseline for cases was the date of MI of the index case in their sibship or mother/father.

The RRs from the Poisson model showed that siblings had a four-fold higher risk of getting an MI than the general population (Figure 2). Further the Poisson model showed that a sister index case lead to an RR of 5.16 [95% confidence interval (CI), 3.33–8.00], P value < 0.001, and a brother index case with an RR of 4.13; 95% CI, 3.31–5.14, P value < 0.001. P value for interaction analysis of gender of the index case was P = 0.37 in the unadjusted analysis and P = 0.22 in the final multivariate analysis.
The RR was 2.40; 95% CI, 2.20–2.60, \( P \) value < 0.001 for children of a maternal index case and 1.98; 95% CI, 1.89–2.01, \( P \) value < 0.001 for children of a paternal index case; \( P \) value for difference <0.0001 in both univariate and multivariate analysis. Offspring of a paternal or maternal index case under the age of 50 years at the time of MI had an RR of 3.30; 95% CI, 2.92–3.72, \( P \) value, 0.001 and 3.23; 95% CI, 2.56–4.10, \( P \) value, 0.001, respectively (Figure 2); \( P \) value for interaction between age (below or above 50 years of age) and paternal index case, 0.0001 in both univariate and multivariate analysis, and \( P = 0.0015 \) in univariate and \( P = 0.18 \) in multivariate analysis between age (below or above 50 years of age) and maternal index case.

Calculations with age of the sibling index case were not possible because only 1375 sibling index cases had MI after the age of 50 years.

The first adjusted analysis included hypertension, hypercholesterolaemia, diabetes, and treatment with aspirin in the model. The RRs were only slightly lowered, most significant for a paternal/maternal index case under the age of 50 years, to an RR of 2.63; 95% CI, 2.33–2.97 and 2.62; 95% CI, 2.23–3.08, respectively.

When including chronic obstructive lung disease, cerebrovascular disease, peripheral vascular disease, and renal disease in the model, RRs were not changed further. Figure 3 displays the fully adjusted results including all variables.

**Discussion**

This nationwide study focused on risk of MI in first-degree relatives of MI patients in Denmark. The main results of the study indicate a significantly higher relative risk for siblings of a patient with MI and for children whose mother have had MI, compared with children whose father had an MI. Notably for children whose parents suffered from an MI before the age of 50, the risk for MI was particularly elevated.

A US study suggested that disease prevalence was lower in offspring of a parental index case than for siblings of a patient with MI, and explained it by clustering of common risk factors for MI. But our multivariate analysis, which accounted for most of the common MI risk factors, demonstrated that only part of the risk could be explained by common risk factors. This sharing of genes and environmental factors might explain the particularly high risk for siblings of a patient with MI. In fact, the common risk factors included in our multivariate analysis only resulted in a modest lowering of the RR, suggesting that other environmental factors, gene–environment interactions of unknown genes may be of importance. The high risk for individuals of an affected mother supports a recent study that investigated sex-specific familial clustering of MI and observed a similarly increased risk. Both children of a maternal case and children of parents affected at young age, might suffer from hereditary disorders, especially if we take the

**Figure 1** Study flowchart of inclusion and exclusion. MI; myocardial infarction.
Carter effect into account. The Carter effect states that the less affected sex would have a higher threshold of disease, which in this particular subject would entail that women need more affected genes to have an MI than men and therefore carry a higher untoward genetic load than men. It is therefore more likely that maternal cases pass on affected genes to their offspring and therefore these infants would have a higher risk. Thus, the affected individuals in our study may carry a higher burden of adverse genotypes, potentially translating this into a higher RR of their siblings. The sex of the sibling index case might be of greater significance in our, since a potentially translating this into a higher RR of their siblings. The sex of the affected individual is severely elevated.

The main limitations of our study were the limited time in which family relations could be determined and the limited time for which information on family history through patient interviews or structured questionnaires, a method prone to recall bias. Furthermore, most other similar studies were case—control studies, and for this particular subject it is almost impossible to find a proper control group.

The strength of our study lies in the fact that it is hitherto the largest on the subject, and that family history and relationships were collected from a nationwide database. Most other studies collected their information on family history through patient interviews or structured questionnaires, a method prone to recall bias. Furthermore, most other similar studies were case—control studies, and for this particular subject it is almost impossible to find a proper control group.

The main limitations of our study were the limited time in which family relations could be determined and the limited time for which diagnoses were available. The identity of parents has been available in Denmark since 1954. This provides the great possibility to study the relation between a parental MI and MI in offspring < 60 years old. For siblings, this means the total number of cases was moderate since the population born after 1954 has not suffered from many infarctions yet. For this reason we were not able to study sibling effects on the age of the first case in the sibship, and the study can therefore only assess the risk of siblings at a young age.

Our study only addressed family relations, not genetics, and we had limited access to risk factors. It would have been preferable to control for smoking and obesity, and further it was not possible to control for socio-economic status, lack of exercise, unhealthy food habits, and chronic stress. These are factors that tend to cluster in families, and might have influence on the MI risk in families. Furthermore, family members to a patient with MI might be more prone to get a health check-up than the rest of the population, but this does not exclude the possibility that the diagnosis of diabetes and hypertension could be under-diagnosed. Statins was not introduced before the early 1990s, which may result in an underestimated prevalence of hypercholesterolaemia in our study during this period. Thus, it is not possible to conclude if the relationships we have found in our study are due to a genetic relation or an environmental factor.

Environmental risk factors are very difficult to assess, and therefore a way to determine a possible genetic factor would be an exon screening in the groups where the familial clustering had the most impact, in example, between mother and child that both suffered from MI.

In conclusion, the first-degree relatives of a patient with an MI have themselves a substantially higher risk of MI. This risk is particularly elevated when the MI case is the mother or a sibling. Also, when the MI case is younger than 50 years, the risk for the children is severely elevated.

#### Table 1 Baseline characteristics of index cases at the time of their myocardial infarction

<table>
<thead>
<tr>
<th>Sibling, n (%)</th>
<th>Paternal, n (%)</th>
<th>Maternal, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 30 years</td>
<td>684 (9.1)</td>
<td>342 (0.4)</td>
</tr>
<tr>
<td>30–40 years</td>
<td>2062 (27.3)</td>
<td>3134 (3.2)</td>
</tr>
<tr>
<td>40–50 years</td>
<td>3431 (45.4)</td>
<td>14 267 (14.8)</td>
</tr>
<tr>
<td>50–60 years</td>
<td>1317 (17.4)</td>
<td>29 277 (30.3)</td>
</tr>
<tr>
<td>60–70 years</td>
<td>58 (0.8)</td>
<td>29 824 (30.9)</td>
</tr>
<tr>
<td>70–80 years</td>
<td>0 (0.0)</td>
<td>16 083 (16.6)</td>
</tr>
<tr>
<td>&gt; 80 years</td>
<td>0 (0.0)</td>
<td>3723 (3.9)</td>
</tr>
</tbody>
</table>

#### Table 2 Baseline characteristics (obtained at the date of the index case’s myocardial infarction) of the first-degree relatives

<table>
<thead>
<tr>
<th>Sibling, n (%)</th>
<th>Paternal offspring, n (%)</th>
<th>Maternal offspring, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 30 years</td>
<td>1876 (16.9)</td>
<td>123 265 (63.4)</td>
</tr>
<tr>
<td>30–40 years</td>
<td>3613 (32.5)</td>
<td>53 456 (27.5)</td>
</tr>
<tr>
<td>40–50 years</td>
<td>4338 (39.0)</td>
<td>16 525 (8.5)</td>
</tr>
<tr>
<td>50–60 years</td>
<td>1248 (11.2)</td>
<td>1258 (0.7)</td>
</tr>
<tr>
<td>60–70 years</td>
<td>48 (0.4)</td>
<td>3 (0.0)</td>
</tr>
<tr>
<td>70–80 years</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>&gt; 80 years</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
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#### Comorbidities

- Diabetes: 123 (1.6) vs 1770 (18.0) vs 1008 (3.5)
- Peripheral vascular disease: 30 (0.4) vs 1643 (1.7) vs 651 (2.2)
- Renal disease: 53 (0.7) vs 665 (0.7) vs 277 (1.0)
- COLD: 27 (0.4) vs 4361 (4.5) vs 1530 (5.3)
- Cerebrovascular disease: 89 (1.2) vs 5455 (5.6) vs 2065 (7.1)
- Use of statins: 750 (9.9) vs 3000 (3.1) vs 1322 (4.5)
- Hypertension: 911 (12.1) vs 7680 (8.0) vs 4530 (15.5)
- Use of aspirin: 705 (9.3) vs 7216 (7.5) vs 3308 (11.3)

COLD, chronic obstructive lung disease.
Conflict of interest: None declared.

References

Figure 2. Unadjusted rate ratios of myocardial infarction in families. The rate ratios of the Poisson model for first-degree family members to the listed index cases, unadjusted. RR, rate ratio.

Figure 3. Adjusted rate ratios of myocardial infarction in families. The rate ratios of the Poisson model for first-degree family members to the listed index cases, adjusted for diabetes, hypertension, use of statins, use of acetyl-salicylic acid, chronic obstructive lung disease, cerebrovascular disease, peripheral vascular disease, and renal disease. RR, rate ratio.
Perforation of the right ventricle by bone cement: a rare complication of kyphoplasty

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A 64-year-old woman was referred to our Department of Cardiology after a cardiac magnetic resonance imaging, ordered for evaluation of chest discomfort, had detected three foreign objects of unknown origin in the right heart (Panel A). After admission, echocardiography (Panels B and C), supplementary material online, Videos S1–S4), chest X-ray (Panel D) and computed tomography (CT) (Panel E) confirmed the presence of three elongated foreign objects with thrombus formation in the right atrium and ventricle. Medical history revealed a balloon kyphoplasty which had been performed for osteoporotic fractures of the lumbar vertebral bodies 1 and 4 two months prior.

Due to the apparent thrombus formation and the patient’s mild symptoms, a regime of oral anticoagulation was started. An attempt to intentionally remove the objects within 4 weeks was scheduled and the patient was discharged. Two weeks later, however, the patient was re-admitted to our emergency department due to progressive dyspnoea and chest discomfort. A repeat CT scan now revealed dislocation of one object with consecutive perforation of the right ventricle and moderate pericardial effusion (Panels F and G). The patient underwent urgent cardiomyotomy on cardiopulmonary bypass and three bone cement filaments were retrieved (Panels H and I). Retrospectively, these filaments originated from the kyphoplasty during which several millilitres of polymethylmethacrylate must have accidentally been injected into a paravertebral vein and subsequently embolized into the vena cava. The postoperative course remained uneventful and the patient fully recovered.

Pulmonary embolism of bone cement has been reported to occur in up to 4.6% of all patients after kyphoplasty. However, physicians should also be aware of the possibility of cardiac complications. If detected, intracardiac foreign bodies should be monitored by repetitive echocardiographic imaging and evacuated in a timely manner.

Supplementary material is available at European Heart Journal online.