Multiplex sibling history of coronary heart disease is a strong risk factor for coronary heart disease

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Aims
Familial risks for coronary heart disease (CHD) in families with multiple affected siblings have not been thoroughly studied. This nationwide cohort study aimed to determine familial risks for hospitalization or death due to CHD in families with multiple affected siblings.

Methods and results
The study is a nationwide follow-up study. The Swedish Multigeneration Register data on 0–76-year-old subjects were linked to Hospital Discharge Register and Cause of Death Register data for 1964–2008. Standardized incidence ratios (SIRs) were calculated for individuals whose siblings were hospitalized or died (without previous hospitalization, i.e. primary fatal cases) due to CHD compared with those whose siblings were not affected. The procedure was repeated for spouses. Among a total of 185 810 cases of hospitalization or death due to CHD, the SIRs for hospitalization and death in the siblings of affected probands were 1.82 (95% CI: 1.27–2.60) and 1.60 (95% CI: 1.10–2.36), respectively. The SIRs for hospitalization in siblings of two and three affected probands were 6.92 (95% CI: 4.77–10.03) and 7.88 (95% CI: 5.31–11.70), respectively. The SIRs for death in siblings of two and three affected probands were 7.31 (95% CI: 4.76–11.19) and 6.61 (95% CI: 3.91–11.10), respectively. Spouses had low overall familial risks (SIR = 1.05, 95% CI: 1.05–1.06).

Conclusion
Family history of multiple affected siblings increases the CHD risk. Family history is not a binary trait. There are degrees of risk associated with family history with more than one affected sibling.

Keywords
Coronary artery disease • Epidemiology • Family history • Risk factors • Mortality

Introduction
Family history of coronary heart disease (CHD) in a first-degree relative has been shown in a large number of studies of parents and offspring and/or siblings1–13 to be an important risk factor for CHD. Moreover, it is an independent risk factor even when adjusting for traditional CHD risk factors such as smoking, hypertension, lipids, overweight, and diabetes.13,12 The risk of CHD has also been studied in twins14,15 and adoptees,16 with the results indicating an important genetic contribution to the familial transmission of CHD. The familial risk of CHD is highest in young monozygotic twins.14,15 Generally the importance of a family history of CHD decreases with age.1–13

The risk of CHD in siblings in multiplex families (two or more affected siblings probands) is less certain because published estimates are derived from only three case-control studies.17–19 Such studies generally lack sibling CHD event validation. We have therefore performed a nationwide family study of hospitalization due to CHD and primary fatal CHD (cases without previous hospitalization for CHD) in siblings, including in multiplex families. The spousal risk was determined to estimate the familial non-genetic contribution.

Methods
This study was approved by the Ethics Committee of Lund University, Sweden. The data set used in this study was constructed by linking several national Swedish registers provided by the Swedish government-owned statistics bureau Statistics Sweden and the National Board of Health and Welfare. The Multi-Generation Register included persons born in Sweden in 1932 and later who were linked to their siblings. Those siblings born 1932 or later constituted the
present study population. Linkages were made to the National Census data in order to ascertain individual-level socioeconomic status. The final link was made by adding individual data from the Swedish Cause of Death Register (1964–2008) and the Swedish Hospital Discharge Register (1964–2008), the latter of which records dates of hospitalization and hospital diagnoses since 1964. All linkages were performed using the individual national identification number that is assigned to each resident in Sweden for their lifetime. This number was replaced by a serial number in order to preserve anonymity. The serial number was used to check that each individual was entered only once (for his or her first diagnosis of CHD). Over 11.8 million individuals in 3.9 million families were included in this database; the oldest (born in 1932) were 76 at the end of the follow-up, which spanned 1964–2008.

Predictor and outcome variables

Coronary heart disease was defined, as previously described,16 21 by the following ICD codes: ICD-7 420; ICD-8 410-414; ICD 9 410-414; and ICD 10 I20-I25 (Supplementary material online, Table S1). A total of 185,810 patients with CHD were identified, based on their first discharge recorded in the Hospital Discharge Register or the main cause of death diagnosis.

Individual variables adjusted for in the analysis

Sex: male or female. Age at diagnosis was categorized into 5-year groups, and the groups were merged as necessary. Socioeconomic status for both males and females was defined by occupation, divided into six socio-economic groups:20–22 (i) farmers, (ii) unskilled/skilled workers, (iii) white-collar workers, (iv) professionals, (v) self-employed workers, and (vi) all non-employed individuals (economically inactive individuals including unemployed individuals and homemakers).20–22 To allow adjustments for regional differences in hospitalization rates, the geographic region of residence was divided into three groups: (i) large city, i.e. Stockholm, Gothenburg, or Malmö; (ii) Southern Sweden; and (iii) Northern Sweden. Spouses were identified for the population over 25 years old based on common children.20–22 Comorbidity was defined as the first hospitalization with a main diagnosis at follow-up (1964–2008) of the following: (i) chronic obstructive pulmonary disease; (ii) obesity; (iii) alcohol misuse; (iv) type 2 diabetes mellitus; and (v) hypertension (Supplementary material online, Table S2). Comorbidity was viewed as a binary variable (comorbidity present: yes or no). Each of the five comorbidities was a separate variable in the model. The number of siblings was categorized into six different groups: 1, 2, 3, 4, 5 and 6 or more siblings.

Statistical analysis

For the analysis of familial risks, the same method was used, as in previous studies.20–22 The cohort method is described in detail by Hemminki et al.23 As previously described, the cohort method takes into account clustering within families, since it is based on complete ascertainment of sibships in affected individuals.23 Person-years at risk (i.e. the number of persons at risk multiplied by the time at risk) were calculated from the start of follow-up on 1 January 1964 until hospitalization or death for CHD, death, emigration, or the end of the follow-up (31 December 2008).23–26 Age-adjusted incidence rates were calculated for the whole follow-up period, divided into 5-year periods.24–26 Standardized incidence ratios (SIRs) were used to measure the relative risk of CHD in individuals with sibling history of CHD (hospitalization or death) compared with individuals with siblings without history of CHD. Similar calculations were performed separately for spouses.

The familial SIRs were calculated as the ratio of the observed (O) and expected (E) numbers of CHD cases using the indirect standardization method:

\[
SIR = \frac{\sum_{j=1}^{l} o_j}{\sum_{j=1}^{l} e_j} = \frac{O}{E^*},
\]

where \( O = \sum o_j \) denotes the total observed number of cases in the study group; \( E^* \) (expected number of cases) is calculated by applying

### Table 1

The number of cases of hospitalization and mortality (without previous hospitalized coronary heart disease) due to coronary heart disease in individuals aged 0–76 years (1964–2008)

<table>
<thead>
<tr>
<th>Region of residence</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large city</td>
<td>53 024</td>
<td>6936</td>
</tr>
<tr>
<td>Southern Sweden</td>
<td>76 639</td>
<td>9011</td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>36 213</td>
<td>3987</td>
</tr>
<tr>
<td>Hospitalization with chronic obstructive pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 441</td>
<td>987</td>
</tr>
<tr>
<td>No</td>
<td>155 435</td>
<td>18 947</td>
</tr>
<tr>
<td>Hospitalization due to alcohol misuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9822</td>
<td>2955</td>
</tr>
<tr>
<td>No</td>
<td>156 054</td>
<td>16 979</td>
</tr>
<tr>
<td>Hospitalization with heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 073</td>
<td>1565</td>
</tr>
<tr>
<td>No</td>
<td>143 803</td>
<td>18 369</td>
</tr>
<tr>
<td>Hospitalization with type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 548</td>
<td>2083</td>
</tr>
<tr>
<td>No</td>
<td>142 328</td>
<td>17 851</td>
</tr>
<tr>
<td>Hospitalization with hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43 032</td>
<td>1766</td>
</tr>
<tr>
<td>No</td>
<td>122 844</td>
<td>18 168</td>
</tr>
<tr>
<td>History of CHD in siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 812</td>
<td>3735</td>
</tr>
<tr>
<td>No</td>
<td>129 064</td>
<td>16 199</td>
</tr>
</tbody>
</table>
stratum-specific standard incidence rates ($\lambda^*$) obtained from the refer-
ence group to the stratum-specific person-years ($n_j$) of risk for the
study group; $a_j$ represents the observed number of cases that
the cohort subjects contribute to the $j$th stratum; and $J$ represents
the strata defined by cross-classification of the following adjustment
variables: age (5-year groups), sex, socioeconomic status, time
period (5-year groups), geographic region of residence, number of sib-
lings, and comorbidities. The 95% confidence intervals (95% CIs)
were calculated assuming a Poisson distribution.

Data values are accurate to two decimals places. All analyses were
performed using the SAS version 9.2 (SAS Institute, Cary, NC, USA).

**Results**

We analysed siblings in Sweden aged 0–76 between 1964 and 2008. A total of 165 876 cases of hospitalization due to CHD and 19 934 primary fatal (death by CHD without previous hospital-
zation for CHD) cases were identified (Table 1). Table 2 shows the
distribution of familial and non-familial cases of hospitalization and
death due to CHD according to the number of siblings (family
size). The left column shows the distribution of non-familial cases (i.e. single cases in families). The right column shows the distri-
bution of familial cases (i.e. two or more cases in a single family).

**Familial siblings risks for coronary
heart disease**

Overall, 40 547 of the 185 810 CHD cases (hospitalization and
death) (22%) were familial (Table 2). Table 3 shows the familial
sibling risks. Of the 165 876 cases of hospitalization due to
CHD, 36 812 (22%) were familial (Table 3). Of the 19 934
primary fatal cases of CHD, 3735 (19%) were familial (Table 3).
The overall familial SIRs for hospitalization due to CHD were
similar for males and females (1.84 and 1.77, respectively) and
were >1 for all age groups up to 69 years. Although the CIs over-
lapped, the SIRs for hospitalization for CHD were higher if the
proband and cases were of the same sex (Supplementary material
online, Table S3). The SIR for hospitalization for CHD was higher
for males (2.02) than females (1.64) if the proband was a male,
and the SIR for CHD was higher for females (2.04) than males
(1.34) if the proband was a female. The familial SIRs tended to
be higher at younger ages. The familial risk for primary fatal
CHD was significant only for males (Table 3).

Table 4 is based on families with two or more cases of CHD.
Individuals with two or more affected siblings accounted for
5.1% of all hospitalized CHD patients and 4.0% of all fatal CHD
cases among siblings. The SIR for hospitalization due to CHD
increased from 1.49 (95% CI: 1.04–2.13) in individuals with one
sibling with CHD to 6.92 (95% CI: 4.77–10.03) when two siblings
were affected (Table 4). When three siblings were affected, the
SIR was 7.88 (95% CI: 5.31–11.70). A similar pattern was observed
for primary fatal cases (Table 4). Supplementary material online,
Table S4 shows familial SIR for CHD by the number of siblings
(family size).

The familial sibling risks were independent of the number of sib-
lings in the family (Supplementary material online, Table S5).
However, the familial risk seemed to be dependent on the propor-
tion of affected siblings in a family (Supplementary material online,
Table S3). For instance, the familial risk of CHD with two affected
siblings was higher in families with 3 (11.27) siblings than in families
with 6 siblings (5.16) (Supplementary material online, Table S5).

**Spousal risk of coronary heart disease**

To evaluate the contribution of environmental sharing to the
observed risks of CHD, SIRs were calculated for spouses of indivi-
duals who suffered hospitalization or death due to CHD. There
was a significant, but modest, increased risk for hospitalization
due to CHD among spouses (SIR = 1.07, 95% CI: 1.07–1.07)
(data not shown in tables). The risk for primary fatal CHD
among spouses was 1.01 (95% CI: 1.00–1.02).

**Sensitivity analysis**

A sensitivity analysis was performed in order to investigate
whether changes of, for example, diagnostic methods, autopsy
rate, smoking, and CHD incidence rate over time may have
affected the familial risks. The familial sibling risks were calculated
separately for the period 1964–88 and for 1989–2008. However,
the CIs in the familial sibling risks for the two periods overlapped,
although the risks were slightly lower during the second period
(Supplementary material online, Table S6).

**Table 2** Distribution of familial and non-familial cases of coronary heart disease according to the number of siblings

<table>
<thead>
<tr>
<th>No. of siblings</th>
<th>Single-case families (non-familial)</th>
<th></th>
<th>Families with 2+ cases (familial)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Families = individuals (n)</td>
<td>%</td>
<td>Individuals (n)</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>36 735</td>
<td>25.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>47 401</td>
<td>32.6</td>
<td>7794</td>
<td>19.2</td>
</tr>
<tr>
<td>3</td>
<td>30 952</td>
<td>21.3</td>
<td>10 023</td>
<td>24.7</td>
</tr>
<tr>
<td>4</td>
<td>15 885</td>
<td>10.9</td>
<td>8323</td>
<td>20.5</td>
</tr>
<tr>
<td>5</td>
<td>7492</td>
<td>5.2</td>
<td>5686</td>
<td>14.0</td>
</tr>
<tr>
<td>6+</td>
<td>6798</td>
<td>4.7</td>
<td>8721</td>
<td>21.5</td>
</tr>
<tr>
<td>All families</td>
<td>145 263</td>
<td>100.0</td>
<td>40 547</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NA, not applicable.
Numbers comprise cases of hospitalization for CHD and primary fatal CHD.
Discussion

This large nationwide familial study of hospitalization due to CHD and primary fatal cases of CHD in Sweden highlights the importance of multiplex sibling history as a predictor of the risk of CHD. The present study demonstrates that family history should not be viewed narrowly as a binary variable (i.e. present or not present). Rather, there are degrees of risk associated with the family history and the risk seems to become quite potent when more than one sibling develops CHD. Previous published studies have been smaller case-control studies. In addition to giving firm risk estimates for multiplex siblings, the present study also presents siblings’ risks of hospitalization for CHD and primary fatal CHD, which is in agreement with previously published

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Familial standardized incidence ratios for coronary heart disease (hospitalization or death) in siblings by the age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>687</td>
</tr>
<tr>
<td>40–49</td>
<td>4720</td>
</tr>
<tr>
<td>50–59</td>
<td>10 776</td>
</tr>
<tr>
<td>60–69</td>
<td>8270</td>
</tr>
<tr>
<td>≥70</td>
<td>1312</td>
</tr>
<tr>
<td>All</td>
<td>25 765</td>
</tr>
</tbody>
</table>

| Death | | | | | | | | |
| <40 | 46 | 1.52 | 0.79–2.87 | 11 | 1.37 | 0.48 | 3.48 | 57 | 1.49 | 0.80–2.73 |
| 40–49 | 304 | 2.08 | 1.31–3.28 | 66 | 1.68 | 0.92 | 3.02 | 370 | 1.99 | 1.27–3.12 |
| 50–59 | 1105 | 1.83 | 1.22–2.74 | 229 | 1.52 | 0.94 | 2.45 | 1334 | 1.77 | 1.18–2.63 |
| 60–69 | 1196 | 1.49 | 1.00–2.23 | 398 | 1.40 | 0.90 | 2.19 | 1594 | 1.47 | 0.99–2.18 |
| ≥70 | 252 | 1.54 | 0.96–2.46 | 128 | 1.50 | 0.88 | 2.52 | 380 | 1.52 | 0.97–2.38 |
| All | 2903 | 1.66 | 1.13–2.44 | 832 | 1.47 | 0.97 | 2.22 | 3735 | 1.61 | 1.10–2.36 |

O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

Family history was defined as at least one affected sibling proband with CHD (hospitalization or death).

Bold type: 95% CI does not include 1.

SIRs were adjusted for age, time period, geographic region of residence, socioeconomic status (occupation), number of siblings, and hospitalization for comorbidities.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Familial standardized incidence ratio for coronary heart disease (hospitalization or death) in siblings by the number of affected sibling probands (hospitalization or death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>One sibling</td>
<td>20 032</td>
</tr>
<tr>
<td>Two siblings</td>
<td>4290</td>
</tr>
<tr>
<td>Three siblings</td>
<td>1074</td>
</tr>
<tr>
<td>Four or more siblings</td>
<td>369</td>
</tr>
</tbody>
</table>

| Death | | | | | | | | |
| One sibling | 2291 | 1.38 | 0.93–2.03 | 656 | 1.21 | 0.79 | 1.85 | 2947 | 1.34 | 0.91–1.96 |
| Two siblings | 471 | 7.21 | 4.65–11.17 | 138 | 7.64 | 4.54 | 12.77 | 609 | 7.31 | 4.76–11.19 |
| Three siblings | 105 | 7.19 | 4.16–12.31 | 26 | 5.00 | 2.30 | 10.36 | 131 | 6.61 | 3.91–11.10 |
| Four or more siblings | 36 | 8.25 | 4.08–16.16 | 12 | 6.35 | 2.31 | 15.74 | 48 | 7.67 | 4.00–14.40 |

O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

Bold type: 95% CI does not include 1.

SIRs were adjusted for age, time period, geographic region of residence, socioeconomic status (occupation), number of siblings, and hospitalization for comorbidities.
studies.1–13 Multiplex sibling history appears to be one of the strongest risk factors for CHD, with a higher relative risk than those for established genetic and acquired risk factors.27–29 The results of the present study show that family history is an important factor to be considered, and might be clinically useful even when the genetics of CHD is better elucidated.30 Interestingly, though multiplex sibling risks is high for CHD, the risk is much lower than among multiplex sibling families with venous thromboembolism (VTE),20 suggesting stronger genetic factors for VTE than CHD. Moreover, VTE and CHD do not appear to share strong genetic risk factors to any large extent, not even among multiplex families.21

Genome-wide association studies (GWAS) have mapped 35 common disease variants to 34 distinct loci.31 Still, these common variants have been estimated to explain only $\approx 8–13\%$ of the total heritability for CHD.31 The situation is similar for most common complex diseases.32 A wide number of explanations are possible for this ‘missing’ heritability, for instance, structural variations (including copy number variants such as insertions and deletions) or rare but strong variants will not be detected in GWAS.31 Many other explanations may exist like epigenetic inheritance, gene–gene interactions, and gene–environment interaction, including epistatic interactions.31,32 The present finding of particularly high risks in multiplex CHD families might be explained by rare but strong variants, gene–gene interactions of two or more variants, or gene–environment interactions, including epigenetic inheritance.

Spouse controls are genetically unrelated, and share an adult environment and similar demographic characteristics except gender.33 Comparison of their family histories is thus matched on many of the factors one might wish to control for in testing a genetic hypothesis.33 Cardiac health-related behaviours such as smoking, exercise, and alcohol consumption correlates much more strongly among spouses than siblings or parent–offspring.34 The slightly increased risk of CHD among spouses suggests that most of the familial risk for CHD is explained by genetic rather than family non-genetic factors, in agreement with published twins and adoptees.14–16 Moreover, the reduced familial sibling SIRs with greater age is striking (Table 3) and indicate genetic factors to be of importance. In fact, even in the face of a complete correlation in exposure among siblings, environmental risk factors with a relative risk of <10 lead to modest familial relative risks (ranging from 1 to 2) and low recurrence risks.35 Similar findings are obtained when familial aggregation of two additive environmental factors is considered.36 No such strong acquired risk factors have yet been described for CHD, suggesting that genetic factors are involved in multiplex sibling families. Thus, the high CHD risks in multiplex families are therefore likely genetic. Genome scanning of multiplex sibling families may be an important option for identifying genetic risk factors.

The present design, focusing on cases of hospitalization and death due to CHD, has potential advantages and disadvantages. We had no access to traditional CHD risk factors like smoking, body mass index, and cholesterol values. We therefore cannot directly analyse if sibling history adds predictive power to the Framingham and Reynolds risk scores (RRSs).36,37 However, we adjusted our models for socioeconomic status (occupation) as a proxy for the socioeconomic environment, which is strongly associated with the primary risk factors for CHD. Adjustment was also made for comorbidities of which some are risk factors for CHD (chronic obstructive pulmonary disease, alcohol misuse, diabetes mellitus type 2, heart failure, and hypertension). Moreover, in a study by Murabito et al.12 adjustment for traditional CHD risk factors such as smoking, diabetes, cholesterol, body mass index, and systolic blood pressure did not substantially attenuate the familial sibling risk. Thus, it is therefore unlikely that the inclusions of these traditional risk factors in the model should attenuate the present study findings to a high extent, especially as the present results has been adjusted for the socioeconomic status and comorbidities. In a multivariable-adjusted model Murabito et al.12 found that the odds ratio for sibling cardiovascular disease (CVD) exceeded that for a parental history of CVD. It is therefore not unlikely that including sibling history and multiplex sibling history in the Framingham and RRSs would increase their predictive values for CHD.36,37 The Framingham risk score (FRS) includes age, sex, levels of total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, and anti-hypertensive therapy to estimate the risk of myocardial infarction and CHD risk.36 The RRS includes traditional risk factors used in the FRS and adds a parental family history of premature CHD and high sensitivity C-reactive protein.37 The RRS has provided a better prediction for CHD in two studies, further underlining the importance of a family history of CHD.37,38

Many limitations involve a non-differential bias. The disadvantages include the selection of inpatients with CHD and the possibility that selective factors in the process of hospitalization operate in a way that favours certain families being hospitalized. The affordability of health care and the likelihood of seeking medical advice are probably not selective factors in Sweden because all residents have equal access to universal health care. The low spousal risk does not support any strong selection bias for hospitalization in certain families.

Some sibling risks were undetected due to hospitalization before the start of the follow-up in 1964. Moreover, the Hospital Discharge Register has only had nationwide coverage since 1987. This may have led to an underestimation or overestimation of the familial SIRs if more or fewer familial cases were lost than non-familial cases. Our estimates of familial SIRs for male and female siblings are, however, similar to previously reported familial risks,1–13 suggesting that our study gives a valid estimate of the familial risks. Moreover, age-specific incidence rates were calculated for the whole follow-up period, divided into five 5-year periods, and adjustment was made for possible changes in the incidence rate over time.

Strengths of the study include complete nationwide coverage in a country with high standards of diagnosis, with diagnoses often being made by specialists during extended examinations in clinics. Importantly, the diagnoses were recorded when patients were discharged from hospital and are thus more likely to be accurate. The Swedish Hospital Discharge Register contains no information about diagnostic procedures, which is a limitation. However, with respect to CHD, the overall diagnostic validity of the Hospital Discharge Register is close to 90%.39 Moreover, the diagnosis of myocardial infarction and angina pectoris in the Swedish Inpatient
Register has been validated and found to be correct in 95% of cases.\textsuperscript{39–41} Since it was possible that the diagnostic methods might have varied between geographic regions, we adjusted for the geographic region of residence in order to minimize this possible source of bias. Only main diagnoses of CHD were used in the present study in order to further increase accuracy. Moreover, the Cause of Death Register has been validated.\textsuperscript{42} We conclude that Swedish death certificate data and mortality statistics for CHD are sufficiently accurate for use in epidemiological studies.

Another important strength of our study is that it was based on hospitalization data and was thus free of selection and recall bias. The Swedish Multigeneration Register and Hospital discharge register are validated sources that have been proved to be reliable in the study of many diseases.\textsuperscript{16,20–22,39–41} Data in the national registers are almost complete. In 2001, personal codes and main diagnoses were missing for only 0.4 and 0.9% of hospitalizations, respectively.\textsuperscript{20–22} Information on the occupational status, retrieved from the National Census records in the database, was 99.2% complete.\textsuperscript{20–22}

In conclusion, the present study establishes the importance of the multiplex sibling history of CHD as one of the strongest known risk factors for CHD. The present study demonstrates that the family history should not be viewed as a binary variable. Rather, there are degrees of risk associated with the family history and the risk is particularly high when more than one sibling develops CHD. Epidemiological studies such as ours may be helpful in designing future genetic studies of CHD, which could also focus on multiplex affected siblings.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: none declared.

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