Venous thromboembolism does not share strong familial susceptibility with coronary heart disease: a nationwide family study in Sweden†

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Aims
This nationwide study aimed to determine whether venous thromboembolism (VTE) shares familial susceptibility with coronary heart disease (CHD).

Methods and results
Data from the Swedish Multigeneration Register for subjects aged 0–76 years old for the period 1964–2008 were linked to the Hospital Discharge Register and Cause of Death Register. Familial risks of VTE and CHD were examined in two ways: risk of CHD in offspring whose parents had been diagnosed with VTE, and risk of VTE in offspring whose parents had been diagnosed with CHD. The analyses were repeated separately for siblings and spouses. In total, 174,768 offspring had CHD and 56,302 VTE. No association between VTE and CHD was observed among siblings. Among offspring, a lower risk of CHD was observed in subjects whose parents had suffered from VTE [standardized incidence ratio (SIR) 0.94 (95% confidence interval (CI) 0.92–0.95)], while offspring of parents with CHD had an increased risk of VTE [SIR 1.03 (95% CI 1.01–1.04)]. In spouses of VTE patients, an increased risk of CHD was observed [SIR 1.02 (95% CI 1.01–1.03)]. Conversely, risk of VTE was increased among spouses of CHD patients [SIR 1.03 (95% CI 1.02–1.03)]. Subanalyses of cases of myocardial infarction and pulmonary embolism/deep venous thrombosis showed similar results.

Conclusion
The familial background of CHD is different from that of VTE. The present study suggests that it is unlikely that shared disease-causing mutations exist to a large extent in the population.

Keywords
Coronary heart disease • Venous thromboembolism • Risk factors • Genetics • Myocardial infarction

Introduction
Venous thromboembolism (VTE) [venous thrombosis and pulmonary embolism (PE)] and thromboembolic arterial diseases [myocardial infarction (MI), coronary heart disease (CHD), ischaemic stroke, and peripheral artery disease] are generally considered to be different entities.1,2 Venous thrombi are mainly composed of red blood cells and fibrin (red clots), while arterial thrombi are mainly composed of platelets (white clots).1,2 The different roles played by fibrin and platelets in venous and arterial thrombosis contribute to the concept that these diseases are separate entities.1,2 However, this view has, in the recent years, been questioned by a number of studies that have found associations between VTE and atherosclerosis and its different thromboembolic manifestations, including MI and CHD.1–6

After the discovery of APC resistance by Dahlbäck et al.7 and the finding that factor V Leiden (R506Q), the mutation that causes APC resistance, is associated with premature MI,8 a large number of studies on this topic have been published. However, association studies of haemostatic factors and MI and CHD have produced varying results.9 Meta-analysis data suggest that factor V Leiden and the prothrombin G20210A mutation, both important risk factors for VTE, are weak risk factors for CHD [relative risks 1.27 (95% confidence interval (CI) 1.10–1.45) and 1.31 (95% CI 1.12–1.52), respectively].9 Family studies have shown that susceptibility to VTE has a heritable basis, with familial risks of
Effect of VTE on familial susceptibility with CHD

approximately 2–3,\textsuperscript{10–14} transmitted in part by several candidate
genes, including factor V Leiden and prothrombin G20210A.\textsuperscript{10–15} However, the risk of MI and CHD in patients with a family
history of VTE has not been determined. Only two studies, both from Norway, have investigated the link between familial history of
MI and risk of VTE,\textsuperscript{16,17} finding family history of MI to be a
risk factor for VTE [odds ratio (ORs) 1.31 (95% CI 1.04–1.65) and
1.3 (95% CI 1.1–1.6), respectively].

The aim of the present study was to determine whether familial
risk factors are shared between CHD and VTE. We hypothesized
that the prothrombotic state associated with family history of
VTE\textsuperscript{10–15} might promote CHD. In this nationwide study, familial
risk of CHD and VTE was analysed in two ways: risk of CHD in off-
spring whose parents had been diagnosed with VTE, and risk of VTE
in offspring whose parents had been diagnosed with CHD. The ana-
lyses were repeated for siblings. To investigate the contribution of
family environment, spouse effects were assessed. Subanalyses
were performed for MI and PE/deep vein thrombosis (DVT).

A novel contribution of the present study is its approach: it was
based on data for the period 1964–2008 from the nationwide
Swedish Cause of Death and Hospital Discharge registers. Use
of data for hospitalized and fatal cases eliminated potential
selection and recall bias. The Swedish Multi-Generation Register
(a family dataset) is a validated data source that has been known
to be reliable in the study of numerous familial diseases, including
VTE and CHD.\textsuperscript{13,14,18–22}

Methods

MigMed 2 Database

This study was approved by the Ethics Committee of Lund University,
Sweden. Data used in this study were retrieved from the MigMed 2
Database (an updated version of the original MigMed Database), main-
tained at the Center for Primary Health Care Research, Lund Univer-
sity/Region Skåne, Malmö.\textsuperscript{13,14,18–22} MigMed 2 is a single database that
contains information on all individuals registered as residents of
Sweden. It contains individual-level information on age, sex, parents,
siblings, children, occupation, region of residence, hospital diagnoses,
and dates of hospital admissions for the period 1964–2008. It also
includes information on country of birth, date of emigration, and
date and cause of death. This unique database was constructed using
several national Swedish data registers, including, but not limited to,
the Swedish National Population and Housing Census (1960–
1990),\textsuperscript{23} the Total Population Register, the Multi-Generation
Register,\textsuperscript{24} the Swedish Hospital Discharge Register (1964–2008),\textsuperscript{25}
and the Cause of Death Register.\textsuperscript{26}

Data in the MigMed 2 Database are remarkably complete. In 2001,
personal numbers were missing in only 0.4% of hospitalizations and
main diagnosis in 0.9% of hospitalizations.\textsuperscript{13,14,18–22} Information on
occupational status, retrieved from the National Census records in
MigMed 2, was 99.2% complete.\textsuperscript{13,14,18–22} The Swedish Hospital Dis-
charge Register was started in 1964, and has had nationwide coverage
since 1987. The Swedish Hospital Discharge Register boasts nearly
90% overall validity.\textsuperscript{25} However, the validity for specific cardiovascular
disorders such as VTE, MI, and stroke is even higher, being around 95%.\textsuperscript{25,27,28}

Statistics Sweden, a Swedish government-owned statistics bureau,
provided the Multigeneration Register, in which offspring (second
generation) born in Sweden since 1932 are linked to their parents
(first generation) shortly after birth. Families can be defined by
linking all children to their parents. The second generation was used
as the study population in the present study. Data were linked to
national census data in order to retrieve information relating to
individual-level socioeconomic status. Finally, the data were linked
to data from the Swedish Hospital Discharge Register and the Cause
of Death Register.

Data were linked using individual personal identification numbers
that are assigned to all persons in Sweden for their lifetime. For
each individual, this number was replaced by a serial number in
order to maintain anonymity. The serial number was used to check
that each individual was only entered once, for his or her first VTE
or CHD diagnosis (as a cause of hospitalization or death). Only main
diagnoses of VTE and CHD were considered to ensure high validity.
Over 11.8 million individuals in 3.9 million families were included in
the constructed database. The second generation contained 8.9
million individuals, the oldest of whom were born in 1932 and
were 76 years old at the end of the study period, which ran from
1 January 1964 until 31 December 2008.\textsuperscript{13,14,18–22}

Outcome variable

Venous thromboembolism and CHD patients, classified according
to different revisions of the World Health Organization International
Classification of Diseases (ICD-7 before 1967, ICD-8 from 1969 to
1986, ICD-9 from 1987 to 1996, and ICD-10 from 1997 onwards)
were identified in the Hospital Discharge Register and the Cause of
Death Register. In agreement with Souto et al.,\textsuperscript{29} and Zöller et al.,
VTE was defined as not only DVT and PE, but also superficial
venous thrombosis and other forms of venous thrombosis.\textsuperscript{13,14,29}

Thus, VTE was defined by the following ICD codes: ICD-7 463, 464,
465, 466, 583.00, 334.40, 334.50, 68.4, and 68.4; ICD-8 450, 451, 452,
453, 671, and 673.9; ICD-9 437G, 451, 452, 453, 451B, 4516, 451W
451C, 451D, 671E, 671F, 671X, 673C, and 639G; and ICD-10 I26, I26.0,
I26.3, I26.6, 180, 181, 182, O222, O223, O225, O228, O229, O870,
O871, O873, O879, O882, O882b, and O807.

The PE/DVT subgroup was defined by the following ICD codes:
ICD-7 465, 468, and 462; ICD-8 450, 451, 673.9, 4510.00, 671.01,
and 671.02; ICD-9 415B, 416W, 673C, 639G, 451B, 671D, and
671E; and ICD-10 I26, O882, O882b, I801, I802, O223, and O871.

Coronary heart disease was defined according to Sundquist and Li\textsuperscript{18}
by the following ICD codes: ICD-7 420; ICD-8 410–414; ICD
9 410–414; and ICD 10 I20–I25. Myocardial infarction was defined by
the following ICD codes: ICD-7 420.1; ICD-8 410; ICD 9 410;
and ICD 10 I21 and I22.

Statistical analysis

Person-years at risk (number of persons at risk multiplied by time at risk)
were calculated from the start of follow-up (1 January 1964) until hospi-
talization for VTE, MI, or CHD, death, emigration or the end of the study
period (31 December 2008). Familial risk in VTE and CHD was exam-
ined in two ways:\textsuperscript{21,20} risk of CHD in offspring, siblings, and spouses of
probands diagnosed with VTE, and risk of VTE in offspring, siblings,
and spouses of probands diagnosed with CHD. The individual variables
for which the analyses were adjusted were sex, age at first diagnosis (in
5-year time periods, allowing adjustment for changes in incidence over
time), socioeconomic status (defined by six occupational groups:
farmers, unskilled/skilled workers, white-collar workers, professionals,
self-employed individuals, and all others), and region of residence
[large city (Stockholm, Gothenburg, or Malmo), Southern Sweden,
and Northern Sweden], the latter allowing adjustment for regional

differences in hospitalization. Standardized incidence ratios (SIRs) were calculated as the ratio of observed and expected number of cases. The expected number of cases was calculated according to sex, 5-year time period, region of residence and socioeconomic status.

The SIRs for offspring and spouses were calculated separately as the ratio of the observed and expected number of VTE cases using the indirect standardization method:

\[
\text{SIR} = \frac{\sum_{j=1}^{J} o_j \cdot \lambda_j^*}{\sum_{j=1}^{J} n_j \cdot \lambda_j^*} = \frac{O}{E^*}
\]

where \( O = \sum o_j \) denotes the total number of observed cases in the study group; \( E^* \) is calculated by applying stratum-specific SIRs (\( \lambda_j^* \)) obtained from the reference group to the stratum-specific person-year (\( n_j \)) experience of the study group; \( o_j \) represents the number of observed cases that the cohort subjects contribute to the \( j \)th stratum; and \( j \) represents the strata defined by cross-classification of the adjustment variables (age/sex/time period/region of residence/socioeconomic status). 95% CIs were calculated assuming a Poisson distribution.

The cohort method was used to calculate sibling risks. All siblings in families of two or more affected siblings constituted cases. They were compared with single-case families using the described person-year calculation. The method is not sensitive to variations in family size or the number of affected individuals in each family. Briefly, we defined a cohort of individuals with at least one affected sibling and computed incidence rates for this cohort over the study period. In families with two or more affected siblings, each affected sibling was included in the cohort (as the sibling of an affected individual). The incidence rates were calculated as follows:

\[
\frac{\sum_{k=0}^{N} n_k}{\sum_{k=1}^{N} p_k + \sum_{k=1}^{N} y_k}
\]

95% CIs were calculated assuming a Poisson distribution and were adjusted for dependence between sibling pairs. The lower limit for each 95% CI was set to 1.

Presented data are accurate to two decimals and highlighted in bold when the 95% CI did not include 1.00. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

### Results

Among offspring, a total of 56 302 patients were diagnosed with VTE (Table 1). A total of 174 768 individuals were diagnosed with CHD and 93 799 with MI (Table 1).

In offspring whose parents (one or both) had been diagnosed with VTE, risk of CHD as well as MI was slightly decreased in both sexes (Table 2). Subanalysis of cases of PE/DVT gave similar results (Supplementary material online, Table S1).

Having a parent with CHD slightly increased the risk of VTE (by 2% in males and 3% in females) (Table 3). Risk of VTE was slightly increased in both males and females with parental MI (by 3% in both sexes) (Table 4). Risk of PE/DVT among offspring of CHD and MI patients was similarly increased (Supplementary material online, Tables S2 and S3).

### Table 1  Number of cases of venous thromboembolism and coronary heart disease in men and women aged 0–76 years

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>PE + DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>17 044</td>
<td>97.0</td>
<td>18 144</td>
<td>97.8</td>
<td>35 188</td>
<td>97.4</td>
</tr>
<tr>
<td>Death</td>
<td>536</td>
<td>3.0</td>
<td>404</td>
<td>2.2</td>
<td>940</td>
<td>2.6</td>
</tr>
<tr>
<td>All</td>
<td>17 580</td>
<td>100.0</td>
<td>18 548</td>
<td>100.0</td>
<td>36 128</td>
<td>100.0</td>
</tr>
<tr>
<td>All VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>26 466</td>
<td>97.7</td>
<td>28 738</td>
<td>98.4</td>
<td>55 204</td>
<td>98.0</td>
</tr>
<tr>
<td>Death</td>
<td>629</td>
<td>2.3</td>
<td>469</td>
<td>1.6</td>
<td>1098</td>
<td>2.0</td>
</tr>
<tr>
<td>All</td>
<td>27 095</td>
<td>100.0</td>
<td>29 207</td>
<td>100.0</td>
<td>56 302</td>
<td>100.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>61 735</td>
<td>86.4</td>
<td>19 581</td>
<td>87.5</td>
<td>81 316</td>
<td>86.7</td>
</tr>
<tr>
<td>Death</td>
<td>9696</td>
<td>13.6</td>
<td>2787</td>
<td>12.5</td>
<td>12 483</td>
<td>13.3</td>
</tr>
<tr>
<td>All</td>
<td>71 431</td>
<td>100.0</td>
<td>22 368</td>
<td>100.0</td>
<td>93 799</td>
<td>100.0</td>
</tr>
<tr>
<td>All CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>112 069</td>
<td>87.9</td>
<td>42 893</td>
<td>90.8</td>
<td>154 962</td>
<td>88.7</td>
</tr>
<tr>
<td>Death</td>
<td>15 469</td>
<td>12.1</td>
<td>4337</td>
<td>9.2</td>
<td>19 806</td>
<td>11.3</td>
</tr>
<tr>
<td>All</td>
<td>127 538</td>
<td>100.0</td>
<td>47 230</td>
<td>100.0</td>
<td>174 768</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Among siblings, no associations between CHD and VTE were observed (Tables 2–4). Subanalyses of MI (Tables 2 and 4; Supplementary material online, Tables S1 and S3) and PE/DVT (Supplementary material online, Tables S1–S3) did not reveal any significant associations among siblings. Moreover, no significant association between CHD and VTE was observed in multiplex families with two affected sibling probands or three or more affected sibling probands with CHD or VTE, respectively (Supplementary material online, Tables S4 and S5).

To investigate the contribution of family environment, spouse effects were assessed. Risk of CHD was slightly increased in spouses of individuals who had been diagnosed with VTE (Table 2), and risk of VTE was slightly increased in spouses of individuals who had been diagnosed with CHD.

Table 2  Familial standardized incidence ratios for coronary heart disease and myocardial infarction in offspring/siblings/spouses of individuals with venous thromboembolism

<table>
<thead>
<tr>
<th>Parent(s) with VTE</th>
<th>Sibling(s) with VTE</th>
<th>Spouse with VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>SIR</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6846</td>
<td>0.97</td>
</tr>
<tr>
<td>All CHD</td>
<td>11805</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2009</td>
<td>0.94</td>
</tr>
<tr>
<td>All CHD</td>
<td>4236</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Both sexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8855</td>
<td>0.97</td>
</tr>
<tr>
<td>All CHD</td>
<td>16041</td>
<td>0.94</td>
</tr>
</tbody>
</table>

SIR and 95% CI values are correct to two decimal places. Bold type: 95% CI does not include 1.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

Table 3  Familial standardized incidence ratios for venous thromboembolism in offspring/siblings/spouses of individuals with coronary heart disease

<table>
<thead>
<tr>
<th>Parent(s) with CHD</th>
<th>Sibling(s) with CHD</th>
<th>Spouse with CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>SIR</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 141</td>
<td>1.02</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 722</td>
<td>1.03</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Both sexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 863</td>
<td>1.03</td>
<td>1.01</td>
</tr>
</tbody>
</table>

SIR and 95% CI values are correct to two decimal places. Bold type: 95% CI does not include 1.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

Table 4  Familial standardized incidence ratios for venous thromboembolism in offspring/siblings/spouses of individuals with myocardial infarction

<table>
<thead>
<tr>
<th>Parent(s) with MI</th>
<th>Sibling(s) with MI</th>
<th>Spouse with MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>SIR</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8511</td>
<td>1.03</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 660</td>
<td>1.03</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Both sexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 171</td>
<td>1.03</td>
<td>1.01</td>
</tr>
</tbody>
</table>

SIR and 95% CI values are correct to two decimal places. Bold type: 95% CI does not include 1.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.
(Table 3). Subanalyses of MI (Tables 2 and 4; Supplementary material online, Tables S1 and S3) and PE/DVT (Supplementary material online, Tables S1–S3) showed similar weak associations in spouses.

A sensitivity analysis including not only main diagnosis but also secondary diagnosis of VTE and CHD was performed. The results were similar to the results above with inclusion of only main diagnosis of VTE and CHD (Supplementary material online, Tables S6–S9). A similar lack of association between CHD and VTE was observed in multiplex families with two or more affected sibling probands with the inclusion of both main and secondary diagnoses of VTE and CHD (Supplementary material online, Tables S8 and S9).

Discussion

To our knowledge, this is the first nationwide attempt to assess the familial risk of CHD in relation to VTE. The lack or only very weak familial aggregation of CHD and VTE, in contrast to the much higher individual familial risks of CHD or VTE only, demonstrates that the familial and genetic backgrounds of these disorders are different. Familial sharing is necessary, though not sufficient, to infer genetic susceptibility. This, together with the weak associations among spouses, reflecting shared environmental familial risk factors, suggests that it is unlikely that shared disease-causing mutations exist to a large extent in the population. It seems paradoxical that the hypercoagulable state associated with familial history of VTE is not a risk factor for CHD, and that among offspring it may even be protective. However, arterial (CHD) and venous (VTE) diseases differ significantly in terms of epidemiology and pathophysiology.

Moreover, increased thrombin generation, which occurs in patients with familial thrombophilia, could under certain conditions (i.e. when thrombin binds to thrombomodulin) have anticoagulant effects balancing its procoagulant effects. In fact, increased levels of F1 + 2 (prothrombin activation fragment) and TAT (thrombin–anthrombin complex), which are markers of thrombin activation and are associated with VTE, were not risk factors for CHD in a prospective study.

Only two other articles have studied the relationship between family history of MI and risk of VTE. In those studies, which were smaller than the present one, family history of MI was found to be a modest risk factor VTE [ORs 1.31 (95% CI 1.04–1.65) and 1.3 (95% CI 1.1–1.6), respectively]. The reverse association was not studied (i.e. effect of family history of VTE on risk of MI). Previous studies focused on DVT and PE, while the present one included all VTE manifestations. However, we also separately calculated risks for MI and PE/DVT to allow comparisons with previous studies. The results for MI and PE/DVT were similar to those for CHD and VTE, respectively.

A meta-analysis found only weak associations between the important VTE risk factors factor V Leiden and prothrombin G20210A and MI and CHD. In fact, genome-wide association studies (GWASs) of MI and CHD have not to date identified any genetic variants that are associated with venous thrombophilia. However, factor V Leiden was confirmed to be a VTE risk factor in a genome-wide analysis. The results of the present epidemiological study are in agreement with the results of GWASs.

The present study has a number of strengths. These include nationwide coverage in a country of high medical standards, and diagnosis of patients by specialists during extended examinations in clinics. In addition, the results were not affected by recall bias because the analyses were based exclusively on diagnosed cases. Importantly, the Multi-Generation Register is a validated source that has been proved to be reliable in the study of many familial diseases.

Data in the MigMed 2 database are almost 100% complete. The study design has been successfully used in a number of studies to determine familial risks for complex diseases, including stroke and VTE.

The present study has a number of limitations. The diagnosis of MI changed during the study period, which may have affected the results for this diagnosis. However, this type of bias should affect other similar studies of familial risks for MI.

The present study covered the 45-year period between 1964 and 2008. However, the Swedish Hospital Discharge Register only contains complete data for the period since 1987. Thus, events that occurred before 1964 and some events that occurred between 1964 and 1986 are missing, which probably creates a non-differential bias regarding familial risks estimates.

Another potential limitation is that we do not have access to the methods used to diagnose patients. However, the Swedish Hospital Discharge register has high validity, especially for cardiovascular disorders, such as VTE, stroke, and MI, for which is approximately 95%.

Only cases in which the main diagnoses were CHD or VTE were analysed to ensure that the analyses were of high quality. This may explain the relatively low numbers of cases of fatal CHD and PE compared with hospitalized cases (Table 1). Moreover, patients hospitalized for VTE or CHD who then died of the same condition were counted as hospitalized cases. A further limitation is that outpatient data were unavailable. However, MI and PE patients are rarely treated as outpatients in Sweden.

Annual numbers of cases of hospital-treated PE were virtually constant between 1987 and 1998. Number of cases of hospital-treated DVT in Sweden declined during the same period. In 1998, 50% of DVT patients in Sweden were treated directly as outpatients. However, incidence rates were calculated for the whole follow-up period, divided into five 5-year periods, and adjustments made for possible changes in incidence rate over time. Another possible limitation is that we had no data for risk factors for VTE or CHD. As a compromise, we adjusted the models for socioeconomic status (occupation).

The results of the present study show that the familial clustering of VTE and CHD is low, which indicates that it is unlikely that shared disease-causing mutations exist to a large extent in the population. Previously reported associations between VTE and CHD may be more related to acquired factors than shared heritable susceptibility.

Supplementary material

Supplementary material is available at European Heart Journal online.
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