Epidemiology and Prevention

Age- and Gender-Specific Familial Risks for Venous Thromboembolism

A Nationwide Epidemiological Study Based on Hospitalizations in Sweden

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Background—This nationwide study sought to determine age- and gender-specific familial risks in siblings hospitalized for venous thromboembolism (VTE).

Methods and Results—The Swedish Multigeneration Register on 0- to 75-year-old subjects was linked to the Hospital Discharge Register for the years 1987–2007. Standardized incidence ratios were calculated for individuals whose siblings were hospitalized for VTE compared with those whose siblings were not affected. Among a total of 45 362 hospitalized cases with VTE, 2393 affected siblings were identified, with a familial standardized incidence ratio of 2.45 (95% confidence interval [CI], 1.66 to 3.61). Gender-specific differences in incidence rates were observed. The familial risks were significantly increased from the age of 10 to 69 years, with a familial standardized incidence ratio of 4.77 (95% CI, 1.96 to 10.83) at ages 10 to 19 years, which decreased to 2.08 (95% CI, 1.35 to 3.20) at ages 60 to 69 years, although the absolute risk increased with age. The familial standardized incidence ratios for siblings with 2 and ≥3 affected probands were 51.87 (95% CI, 31.47 to 85.00) and 53.69 (95% CI, 25.59 to 108.50), respectively. Spouses had low familial risks (standardized incidence ratio=1.07; 95% CI, 1.04 to 1.10; observed spouse cases=3900).

Conclusions—Familial factors, although influenced by age and gender, are important risk factors for VTE. The present study shows that VTE is aggregated in families and suggests that uncovering the sources of familial aggregation (genetic and nongenetic) may be worthwhile. Moreover, in a small fraction of siblings, the familial risk was very high, suggesting segregation of rare but strong genetic risk factors. (Circulation. 2011;124:1012-1020.)

Key Words: epidemiology ■ pulmonary embolism ■ risk factors ■ thrombosis ■ veins

Venous thromboembolism (VTE) is a major medical health problem, with ≈1 per 1000 individuals affected per year.1-3 Acquired risk factors for VTE include immobilization, surgery, trauma, pregnancy, puerperium, lupus anticoagulant, malignant disease, and oral contraceptives.4 Familial thrombophilia (eg, clustering of VTE) was recognized at the beginning of the 19th century.5 Like many common human diseases and traits that cluster in families, VTE is considered a complex disorder influenced by several genetic and environmental factors.4 Heritability of VTE has been estimated to be ≈50% to 60%.6-8 Deficiencies of the natural anticoagulant inhibitors antithrombin, protein C, and protein S have all been associated with familial thrombophilia.4,9 They increase the risk of thrombosis ≈10-fold in heterozygotes.4,8 However, these defects are rare and are found in <1% of the population. Two additional common gene defects, activated protein C resistance due to factor V Leiden and the prothrombin 20210A mutation, have also been associated with familial thrombophilia.4,5 They increase the risk of thrombosis ≈3- to 8-fold in heterozygotes. The prevalence in the white population of the activated protein C resistance and prothrombin 20210A mutations is 5% to 10% and 2% to 3%, respectively. The predictive value of family history for detecting any of these 5 major genetic risk factors is low, however,10-15 suggesting that other genetic or nongenetic familial factors may be important. Few researchers have studied the association of familial history and risk of VTE.15-17 In 3 case-control studies, family history increased the risk for venous thrombosis by ≈2.5-fold, with odds ratios of 2.2, 2.3, and 2.7, respectively.15-17

Editorial see p 996
Clinical Perspective on p 1020

The influence of age and sex on the heritability of VTE has not yet been fully established. Age itself is one of the most important risk factors for VTE, as reviewed by White.18 The incidence rate is lowest among children aged <15 years (<5 per 100 000 person-years) and increases exponentially with age to values in the range of 450 to 600 per 100 000 person-years among individuals aged >80 years.1 Results are
divergent in regard to gender differences.\textsuperscript{18} Silverstein et al\textsuperscript{1}\ observed a slightly higher incidence rate among younger women and a modestly higher risk among older men. In contrast, other researchers found similar incidence rates for VTE in both sexes.\textsuperscript{1,2}

Today, attention is directed toward genome-wide association studies attempting to identify genetic variants associated with VTE rather than the more traditional family studies.\textsuperscript{19–21} For the planning of gene identification studies, it is important for the familial risks to be characterized in detail and for the genetic and environmental components to be delineated. Moreover, familial risk could be of clinical use in identifying individuals with an increased risk for VTE. The novel contribution of this study is partly its approach; it was based on a nationwide register of all hospitalizations in Sweden between 1987 and 2007. Use of hospitalized cases eliminated potential self-report and recall bias. The Swedish family data set (ie, the Multigeneration Register) is a validated source that has been proven to be reliable in the study of many familial diseases.\textsuperscript{22–26}

In this nationwide study, we analyzed the familial risks of hospitalization for VTE among siblings according to age and gender, which has not been determined before.

Methods

This study was approved by the Ethics Committee of Lund University, Sweden. The VTE research database used for this study was constructed by linking several national Swedish registers based on the MigMed 2 database at the Center for Primary Health Care Research, Lund University, Malmö, Sweden. Statistics Sweden, the Swedish government-owned statistics bureau, provided the Multigeneration Register in which persons (from the second generation) born in Sweden in 1932 and later are linked to siblings, which constituted the present study population. Linkages were made with National Census Data to ascertain individual socioeconomic status. The final link was made by adding individual data from the Swedish Hospital Discharge Register, which records complete data on all discharges with dates of hospitalization and diagnoses since 1986. All linkages were performed with the use of an individual national identification number that is assigned to each individual in Sweden for their lifetime. This number was replaced by a serial number for each person to preserve anonymity. The serial number was used to check that each individual was entered only once for his or her first appearance with a VTE diagnosis. More than 1.18 million individuals in 3.9 million families were included in this database; 8.9 million individuals belonged to the second Swedish-born generation in which the oldest born in 1932 had reached age 75 years at the end of the follow-up, which spanned from 1987 to 2007.\textsuperscript{26} A total of 45 362 cases hospitalized for VTE belonged to the second generation.

Outcome Variable

VTE patients were retrieved from hospital discharge records, reported according to the ninth (1987–1996) and 10th (1997–2007) versions of the \textit{International Classification of Diseases} (ICD). VTE was defined as the following ICD-9 numbers according to de Souto et al\textsuperscript{6}: pulmonary embolism (ICD-9: 415B, 416W and ICD-10: I26), superficial or deep phlebitis or thrombophlebitis (ICD-9: 451 and ICD-10: 180), portal vein thrombosis (ICD-9: 452 and ICD-10: 181), other venous embolism or thrombosis (ICD-9: 453 and ICD-10: 182), cerebral venous thrombosis and cerebral infarction due to cerebral vein thrombosis (ICD-9: 437G and ICD-10: I63E, I676), pregnancy-related VTE (ICD-9: 671C, 671D, 671E, 671F, 671X, 673C and ICD-10: O222, O223, O225, O228, O229, O870, O871, O873, O879, O882), or abortion-related VTE (ICD-9: 639G and ICD-10: O082, O087). There is no official translation from ICD-9 to ICD-10. For this reason, deep venous thrombosis before delivery, code 671C in ICD-9, was defined by a grouping of ICD-10 codes (O223, O228, O871), chosen to correspond as closely as possible to the previous 671C code in ICD-9, in agreement with the Swedish National Board of Health and Welfare ICD-9 to ICD-10 translator. A total of 45 362 patients were identified on the basis of their first discharge recorded in the Hospital Discharge Register.

Individual Variables Included in the Analysis

Gender was categorized as male and female subjects. Age at diagnosis was categorized into 5-year groups, and the groups were merged as necessary. Socioeconomic status for both male and female subjects was divided into 6 groups according to occupation, as follows: (1) farmers, (2) unskilled/skilled workers, (3) white-collar workers, (4) professionals, (5) self-employed, and (6) all others.\textsuperscript{22–26} Geographic region was divided into 3 groups: large cities (ie, Stockholm, Gothenburg, and Malmö); (2) Southern Sweden; and (3) Northern Sweden, allowing adjustments for regional differences in hospitalization. Spouse was defined for the population aged \( \geq 25 \) years on the basis of common children.\textsuperscript{22–26}

Statistical Analysis

For the analysis of familial risks, appropriate methods of cohort studies were used, similar to our previous studies.\textsuperscript{22–26} Person-years (ie, the number of persons at risk multiplied by the time at risk) were calculated from the start of follow-up on January 1, 1987, until hospitalization for VTE, death, emigration, or closing date of December 31, 2007.\textsuperscript{27–29} Age-adjusted incidence rates based on the European standard population\textsuperscript{30} were calculated for the whole follow-up period, divided into 5-year periods.\textsuperscript{27–29} Familial risks were calculated for male and female subjects with siblings affected with VTE compared with male and female subjects whose siblings were not affected by these conditions. Standardized incidence ratios (SIRs) were used to measure the relative risk for siblings with a sibling history of VTE compared with siblings without a sibling history of VTE. The same approach was used for spouses.

The SIR for spouses was calculated as the ratio of observed (\( O \)) to expected number of VTE cases with the use of the indirect standardization method, as specified:

\[
SIR = \frac{\sum_{j=1}^{J} \frac{O_j}{E_j}}{\sum_{j=1}^{J} \frac{N_j}{E_j}}
\]

where \( O = \sum o_j \) denotes the total observed number of cases in the study group (affected spouses with spouse history of VTE); \( E^* \) is calculated by applying stratum-specific standard incidence rates (\( \lambda \)) obtained from the reference group (spouses without spouse history of VTE) to the stratum-specific person-year (\( n_j \)) experience of the study group. \( o_j \) represents the observed cases that the cohort subjects contribute to the \( j \)th stratum, and \( J \) represents the strata defined by the cross-classification of various adjustment variables including age (5-year groups), sex, socioeconomic status, period (5-year groups), and region.\textsuperscript{27–29} Confidence intervals (CIs) at a 5% level were calculated with assumption of a Poisson distribution.\textsuperscript{29}

For calculation of sibling risks, the cohort method was used as described.\textsuperscript{25} In this method, all siblings in families of \( \geq 2 \) affected siblings contribute cases, and they are compared with single-case families with the use of 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 1 affected sibling and computed the incidence rates in this cohort over the study period. In a family with \( \geq 2 \) affected siblings, each affected individual is included in the cohort (as the sibling of an affected individual). The incidence rates in the cohort method are given by the following formula:

\[
\sum_{k=1}^{n_k} \frac{n_k}{\sum_{j=1}^{J} n_j}
\]

where \( n_k \) is the number of affected individuals with \( k \) affected siblings, and \( p_k \) the number of person-years contributed by unaffected
individuals in families with \( k \) affected siblings, and \( y_k \) the number of person-years contributed by affected siblings in families with \( k \) affected siblings, in the relevant age/sex/period/region/socioeconomic status category. The corresponding reference rates are given by the following:

\[
\frac{\sum_{i=1}^{n} n_i}{\sum_{i=1}^{n} p_k + \sum_{i=1}^{n} y_i}
\]

CIs were calculated with assumption of a Poisson distribution, and they were adjusted for dependence between the sibling pairs.\(^{25}\) Lower limits of 95% CIs were quoted as 1.\(^{31}\)

The results are shown with 2 decimals and are shown in the tables with an asterisk if the lower CI did not include 1.00 (ie, 2 decimals were considered). All analyses were performed with the use of the SAS statistical package (version 9.1; SAS Institute, Cary, NC).

### Results

We analyzed risks for siblings aged 0 to 75 years hospitalized for VTE in Sweden between 1987 and 2007. The total follow-up period was 132 222 639 person-years. The follow-up period was 130 659 134 person-years for individuals without a sibling history of VTE and 1 563 505 person-years for individuals with a sibling history of VTE. A total of 45 362 patients, 48.5% (\( n=22 004 \)) male and 51.5% female (\( n=23 358 \)), were diagnosed at a mean age of 50.7 years for males and 46.6 years for females. Figure 1 and Table 1 show age-specific incidence rates for males and females. The total incidence rate was significantly higher for females (36.2 per 100 000 years) compared with males (32.5 per 100 000 years) \((P<0.001)\). However, for females aged 10 to 40 years, the total incidence rate was higher than for males, whereas for

<table>
<thead>
<tr>
<th>Age at Diagnosis, y</th>
<th>All</th>
<th>With Sibling History of VTE</th>
<th>All</th>
<th>With Sibling History of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>IR</td>
<td>95% CI</td>
<td>n</td>
</tr>
<tr>
<td>&lt;10</td>
<td>67</td>
<td>0.6</td>
<td>0.5 0.8</td>
<td>0</td>
</tr>
<tr>
<td>10–19</td>
<td>304</td>
<td>2.7</td>
<td>2.4 3.0</td>
<td>3</td>
</tr>
<tr>
<td>20–29</td>
<td>1224</td>
<td>11.0</td>
<td>10.4 11.6</td>
<td>37</td>
</tr>
<tr>
<td>30–39</td>
<td>2406</td>
<td>21.5</td>
<td>20.6 22.3</td>
<td>96</td>
</tr>
<tr>
<td>40–49</td>
<td>4863</td>
<td>44.7</td>
<td>43.5 46.0</td>
<td>303</td>
</tr>
<tr>
<td>50–59</td>
<td>7267</td>
<td>85.2</td>
<td>83.2 87.1</td>
<td>482</td>
</tr>
<tr>
<td>60–69</td>
<td>5107</td>
<td>150.4</td>
<td>146.3 154.5</td>
<td>297</td>
</tr>
<tr>
<td>≥70</td>
<td>766</td>
<td>235.2</td>
<td>218.5 251.8</td>
<td>34</td>
</tr>
<tr>
<td>All</td>
<td>22 004</td>
<td>32.5</td>
<td>32.1 33.0</td>
<td>1252</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism; IR, incidence rate; and CI, confidence interval.
age >50 years, the incidence rate was higher for males. The lowest incidence rates were for children aged <10 years, with 0.6 per 100,000 for males and 0.5 per 100,000 for females (Figure 1 and Table 1). Except for the notch on the female incidence curve at fertile ages, the incidence rates increased exponentially with age for both sexes. At the age of 70 to 75 years, the incidence rates were 235.2 per 100,000 person-years for males and 213.6 per 100,000 person-years for females.

**Familial Risks for Venous Thromboembolism**

In a total of 45,362 hospitalized cases with VTE, there were 2,393 sibling cases (5.3%). Table 1 shows the age-specific familial incidence rates for males and females. Table 2 shows the distribution of familial and nonfamilial hospitalized cases and families according to number of siblings (family size). The left columns show the distribution of the nonfamilial cases (ie, single cases without affected siblings). The right columns show the distribution of the familial cases (ie, families with ≥2 cases). Figure 2 shows the familial and nonfamilial age-specific incidence rates for males and females. Both familial and nonfamilial incidence rates were higher for females than for males at age 10 to 40 years. At age 40 to 49 years, the incidence rates were similar for males and females. At age >50 years, both familial and nonfamilial incidence rates were higher for males than for females. No familial cases were observed for children aged <10 years (Table 3). The overall familial SIR was similar for males and females (SIR, 2.52 versus 2.37). In ages between 10 and 69 years, the familial SIRs were significantly increased in all age intervals. However, the familial SIR was highest among siblings aged 10 to 19 years and decreased with age to 2.08 at age 60 to 69 years. There was also a tendency for increased SIRs for the oldest siblings aged 70 to 75 years (SIR = 1.72; 95% CI, 0.95 to 3.61), which did not reach statistical significance, perhaps because only 70 familial cases were found among 70- to 75-year-old siblings. Although the familial SIRs decreased with age, the absolute risk increased with age and was the highest among those aged 70 to 75 years.

Tables 4 and 5 are based on the data from the right columns (ie, families with ≥2 cases). The SIR for VTE increased from 2.45 (95% CI, 1.66 to 3.61) in singleton siblings to 51.87 (95% CI, 31.47 to 85.00) when 2 siblings were affected probands (n = 177) (Table 4). When ≥3 siblings were affected probands (n = 30), the SIR was 53.69 (95% CI, 25.59 to 108.50). The SIRs were higher, although not significantly so, for male than for female siblings with ≥2 affected probands. These patients with ≥2 affected probands accounted for only 0.46% of all VTE patients among siblings. Table 5 shows familial SIR for VTE by number of siblings in families (family size). For calculation of family risks in siblings, the cohort method used is not sensitive to variations in family size, which is illustrated in Table 5.

We tested for heterogeneity of the familial risks for the different manifestations of VTE in siblings. However, the familial risks were similar for pulmonary embolism (2.28; 95% CI, 1.50 to 3.45), deep or superficial thrombosis of the lower extremities (2.65; 95% CI, 1.77 to 3.97), and other forms of venous thrombosis (2.45; 95% CI, 1.58 to 3.80). Moreover, the familial risks for superficial thrombophlebitis (2.63; 95% CI, 1.55 to 4.43) and deep venous thrombosis (2.70; 95% CI, 1.78 to 4.08) were similar.

Two kinds of analyses were performed to test for the extent of environmental sharing in the observed risks of VTE. First, SIRs for siblings according to age difference were calculated. Overall, the age difference had little effect. Siblings with a difference in age of <5 years showed a SIR of 2.38 (95% CI, 1.94 to 2.62) compared with 2.51 (95% CI, 1.68 to 3.75) for those with a difference of ≥5 years. Second, risks were calculated for spouses hospitalized for VTE. There was a significant but small increased risk for VTE among spouses, with the SIR being 1.07 (95% CI, 1.04 to 1.10; observed spouse cases = 3900).

**Discussion**

This large nationwide familial study of hospitalized cases of VTE in Sweden highlights the value of sibling history as a predictor of the risk of VTE. The family history of siblings appears to be an important risk factor for VTE with a higher relative risk than for many identified genetic risk factors. For many complex diseases, the average familial risks in first-degree relatives is ~2, which is in agreement with the present study. Although a familial risk of ~2 might appear modest, it suggests that uncovering genetic and nongenetic sources of familial aggregation might be worthwhile. Moreover, the dissected underlying familial risk factors (genetic or nongenetic) are likely to have a magnitude that is stronger than the familial risk itself. The 5 major identified genetic risk factors contribute to only ~30% of the family history. The newly identified common, but much weaker, alleles probably contribute to only a small fraction of the familial risks. It has been estimated that 10 additive alleles, each with a genotype relative risk of 2.0 and an allele frequency of 0.1, will only explain a familial risk of 1.06. If multiplicative gene-gene interactions are present, the same 10 alleles will still only explain a familial risk of 1.2. Many newly identified alleles have an estimated genotype relative risk of <1.5. An additive allele with an allele frequency of 0.1 and a genotype risk of 1.5 explains only a familial risk of 1.01. Thus, the overall familial risk of 2.45 in our study is most likely explained in <50% by the alleles known today to be associated with VTE. Thus, in clinical practice, the family history may be more

### Table 2. Distribution of Familial and Nonfamilial Hospitalized Cases and Families According to Number of Siblings (Family Size)

<table>
<thead>
<tr>
<th>No. of Siblings</th>
<th>Single-Case Families (Nonfamilial)</th>
<th>≥2-Case Families (Familial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals, n (%)</td>
<td>Families, n (%)</td>
<td>Individuals, n (%)</td>
</tr>
<tr>
<td>1 sibling</td>
<td>8229 (19)</td>
<td>8229 (19)</td>
</tr>
<tr>
<td>2 siblings</td>
<td>14,717 (34)</td>
<td>14,717 (34)</td>
</tr>
<tr>
<td>≥3 siblings</td>
<td>20,023 (47)</td>
<td>20,023 (47)</td>
</tr>
<tr>
<td>All families</td>
<td>42,969 (100)</td>
<td>42,969 (100)</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
useful for risk assessment than testing for the presently identified alleles associated with VTE.

Our study is the first nationwide one demonstrating an increased familial risk among subjects aged 10 to 69 years but not in those aged <10 years. No significant difference in the magnitude of familial SIRs was observed for males and females, indicating that familial factors are important in both sexes, although the incidence rates for both familial and nonfamilial cases were higher for younger females and higher for older males. The effect of age and gender on the SIRs of siblings has not been determined before in a nationwide study. Thus, no previous studies similar to ours were available for comparison. However, the odds ratios for the family history (any parents, brothers, or sisters affected) as a risk factor for deep venous thrombosis have been estimated in a case-control study. The odds ratios decreased with age from 3.2 at age 18 to 29 years to 2.2 at age 60 to 69 years, in accord with our results. Divergent results regarding the influence of gender on the overall incidence rates in nonfamilial cases have been cited in the literature. The incidence rate for familial cases has not been determined. Our study is in agreement with a previous report from Silverstein et al that

Figure 2. Age-specific incidence rates of venous thromboembolism in siblings with and without a familial sibling history.
found an increased incidence rate among young women and a modest increase in men at older ages. Another interesting finding is that the familial SIRs decreased in magnitude with age but remained significant. Thus, familial factors are also important at older ages.

The highest familial risks of 51.87 and 53.69 were observed for siblings who had 2 and 3 affected probands, respectively. Together, these patients accounted for only 0.46% of all siblings. The high risks are in the order of magnitude of observed risks among individuals with combined prothrombotic genetic defects, such as homozygous activated protein C resistance mutation or the combination of heterozygous activated protein C resistance mutation and protein C, protein S, or antithrombin deficiency. However, whether there are any other rare thrombotic genetic defects other than deficiencies of the natural inhibitors antithrombin, protein S, and protein C remains to be determined. Genome scanning of large thrombophilic families may be an important option for identifying such risk factors.

The low incidence rate in children aged <10 years in our study was similar to those in previous reports. The lack of familial cases among children aged <10 years could be due to the small number of cases, but it could also reflect the fact that the risk is very low even among familial cases and that in most children aged <10 years, 1 or more acquired risk factors, such as cancer, infection, congenital heart disease, and a central venous catheter, are necessary to provoke VTE. Our results are in agreement with family studies of already identified genetic risk factors such as deficiencies of protein C and protein S, in which thrombosis is seldom manifested before age 10 years.

The slightly increased risk for VTE among spouses, with a SIR of 1.07 (95% CI, 1.04 to 1.10), suggests that most of the familial risk for VTE is explained by genetic rather than family environmental factors. Moreover, age difference between siblings did not affect the familial SIR risks, which further supports the finding of a lack of any major familial environmental effect. Thus, our data suggest the view that most of the familial risks observed in our study are genetic, in agreement with a published Danish twin study.

The present design with focusing of the study on hospitalized cases of VTE has potential advantages and disadvantages. However, many of the limitations in the study involve a nondifferential bias. The disadvantages include the reduction in the number of cases and the possibility that some selective factors operate in the process of hospitalization to favor siblings being hospitalized. Affordability of healthcare is probably not a selective factor in Sweden, nor is the likelihood of seeking medical advice important because of equal access to primary and hospital care. Hospitalizations for VTE and other conditions often require a physician’s referral from primary care. Thus, each hospitalized patient is often seen by 2 physicians, of which the physician in the hospital is often a specialist. The low spouse correlation does not

### Table 3. Familial Standardized Incidence Ratios for Venous Thromboembolism in Siblings by Age at Diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis, y</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
<th>All</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>3</td>
<td>2.97</td>
<td>0.40</td>
<td>12.42</td>
<td>14</td>
<td>5.49*</td>
<td>2.11*</td>
<td>13.05*</td>
<td>17</td>
<td>4.77*</td>
<td>1.96*</td>
</tr>
<tr>
<td>20–29</td>
<td>37</td>
<td>4.34*</td>
<td>2.16*</td>
<td>8.47*</td>
<td>75</td>
<td>3.66*</td>
<td>2.04*</td>
<td>6.49*</td>
<td>112</td>
<td>3.86*</td>
<td>2.25*</td>
</tr>
<tr>
<td>30–39</td>
<td>96</td>
<td>3.19*</td>
<td>1.83*</td>
<td>5.51*</td>
<td>113</td>
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<td>4.49*</td>
<td>209</td>
<td>2.87*</td>
<td>1.76*</td>
</tr>
<tr>
<td>40–49</td>
<td>303</td>
<td>3.03*</td>
<td>1.91*</td>
<td>4.79*</td>
<td>248</td>
<td>2.49*</td>
<td>1.55*</td>
<td>3.98*</td>
<td>551</td>
<td>2.76*</td>
<td>1.79*</td>
</tr>
<tr>
<td>50–59</td>
<td>482</td>
<td>2.52*</td>
<td>1.63*</td>
<td>3.90*</td>
<td>396</td>
<td>2.29*</td>
<td>1.47*</td>
<td>3.58*</td>
<td>878</td>
<td>2.41*</td>
<td>1.60*</td>
</tr>
<tr>
<td>60–69</td>
<td>297</td>
<td>2.05*</td>
<td>1.29*</td>
<td>3.25*</td>
<td>259</td>
<td>2.12*</td>
<td>1.32*</td>
<td>3.39*</td>
<td>556</td>
<td>2.08*</td>
<td>1.35*</td>
</tr>
<tr>
<td>≥70</td>
<td>34</td>
<td>1.67</td>
<td>0.82</td>
<td>3.30</td>
<td>36</td>
<td>1.76</td>
<td>0.87</td>
<td>3.45</td>
<td>70</td>
<td>1.72</td>
<td>0.95</td>
</tr>
<tr>
<td>All</td>
<td>1252</td>
<td>2.52*</td>
<td>1.69*</td>
<td>3.77*</td>
<td>1141</td>
<td>2.37*</td>
<td>1.58*</td>
<td>3.56*</td>
<td>2393</td>
<td>2.45*</td>
<td>1.66*</td>
</tr>
</tbody>
</table>

SIR indicates standardized incidence ratio; CI, confidence interval.

*95% CI does not include 1.00.

### Table 4. Familial Standardized Incidence Ratio for Venous Thromboembolism in Siblings by Number of Affected Siblings (Probands)

<table>
<thead>
<tr>
<th>No. of Affected Siblings (Probands)</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
<th>All</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1 proband sibling</td>
<td>1136</td>
<td>2.33*</td>
<td>1.55*</td>
<td>3.49*</td>
<td>1050</td>
<td>2.22*</td>
<td>1.47*</td>
<td>3.33*</td>
<td>2186</td>
<td>2.27*</td>
<td>1.54*</td>
</tr>
<tr>
<td>2 proband siblings</td>
<td>99</td>
<td>63.42*</td>
<td>36.45*</td>
<td>109.22*</td>
<td>78</td>
<td>42.13*</td>
<td>23.54*</td>
<td>74.38*</td>
<td>177</td>
<td>51.87*</td>
<td>31.47*</td>
</tr>
<tr>
<td>≥3 proband siblings</td>
<td>17</td>
<td>59.59*</td>
<td>24.49*</td>
<td>135.21*</td>
<td>13</td>
<td>47.53*</td>
<td>17.82*</td>
<td>115.28*</td>
<td>30</td>
<td>53.69*</td>
<td>25.59*</td>
</tr>
<tr>
<td>All</td>
<td>1252</td>
<td>2.52*</td>
<td>1.69*</td>
<td>3.77*</td>
<td>1141</td>
<td>2.37*</td>
<td>1.58*</td>
<td>3.56*</td>
<td>2393</td>
<td>2.45*</td>
<td>1.66*</td>
</tr>
</tbody>
</table>

SIR indicates standardized incidence ratio; CI, confidence interval. The risks in males and females were calculated without taking the sex of the probands into account.

*95% CI does not include 1.00.
support any strong selection bias for hospitalization of certain families.

Because the follow-up period was 21 years, some sibling pairs were lost because one of the pairs was hospitalized before the start of the follow-up in 1987. This can lead to an underestimation or overestimation of the familial SIR if more or fewer familial cases are lost than nonfamilial cases and they are not in proportion to the estimated familial SIRs. Our total estimates of familial SIRs for males and females of 2.37 and 2.49 are similar to the reported odds ratios of 2.2, 2.3, and 2.7 for the risk of venous thrombosis due to a family history of VTE, suggesting that our study gives a valid estimate of the familial risks in siblings. One explanation could be the high risk of recurrent VTE. Thus, many lost siblings will eventually be affected by a thrombotic event during the follow-up period between 1987 and 2007 and classified as thrombotic cases. Another potential nondifferential bias is the introduction of low-molecular-weight heparin and the treatment of many deep venous thrombosis patients as outpatients. However, age-specific incidence rates were calculated for the whole follow-up period, divided into five 5-year periods, and an adjustment was done for the possibility of changes in the incidence rate over time. A number of less severe thrombotic cases are treated as outpatient cases. If familial cases tend to be more severe than nonfamilial ones, this could overestimate the VTE risk, but there is no evidence supporting this hypothesis. However, under any circumstances, our data will reflect the risk for severe hospitalized cases.

The advantages include complete nationwide coverage in a country with a high standard in the medical diagnosis of siblings, often by a specialist during extended examinations in the clinic. Importantly, the diagnoses are those with which the patients are discharged and are thus accurate. The Swedish Hospitalization Discharge Register contains no information about diagnostic procedures, which is a limitation, but it would be a nondifferential bias. However, with respect to VTE, the overall diagnostic validity of the Swedish Inpatient Register is close to 90%. Moreover, the diagnosis of VTE in the Swedish Inpatient Register has been validated and found to be correct in 95% of VTE diagnoses. In addition, in 91% of cases, VTE is diagnosed by an objective method. This is in agreement with a recent Swedish study demonstrating that VTE is seldom diagnosed without objective investigations. Because it is possible that the diagnostic methods might have varied between geographic regions, we adjusted for geographic region to minimize this possible bias. The high quality of the Swedish Inpatient Register for VTE is in agreement with studies that have found a validity of 95% for stroke and myocardial infarction. Only a main diagnosis of VTE was used in the present study to further increase the accuracy.

An important advantage of our study is that it is nationwide and based on all hospitalized patients without the risk of selection or recall bias. The Swedish family data set (ie, the Multigeneration Register) is also a validated source that has been proven to be reliable in the study of many familial diseases. Data in the MigMed Database are almost complete. In 2001, personal code numbers were missing in only 0.4% and the main diagnosis in 0.9% of hospitalizations. Information on occupational status, retrieved from the national census records in the database, was 99.2% complete. Because environmental risk factors were not available, we adjusted for socioeconomic status (occupation) in the models as a proxy for socioeconomic environment. The lack of major risk factors is a potential confounder, but it is most likely a nondifferential bias. Moreover, major risk factors do not appear to affect the overall familial risk and are not usually included when familial risks are estimated.

In our study, siblings were not excluded because of cancer or any other disease, in agreement with the study by Bezemer et al, a practice that is otherwise common when familial risks are studied. Thus, our data reflect the total impact of a familial history of VTE in the whole population of Swedish siblings. Another possible strength of our study is that we included not only cases of deep venous thrombosis but also superficial thrombophlebitis, pulmonary embolism, and rare manifestations of venous thrombosis such as cerebral sinus thrombosis, representing the whole spectrum of thrombotic manifestations. This definition of VTE could also be a potential limitation if the genetic background is different for different manifestations. However, this definition of VTE has been used by Souto et al and is common in studies of familial thrombophilia. We tested for heterogeneity of familial risks, but no differences were observed for the different manifestations of VTE. Our total estimate of familial SIRs is similar to those reported for risk of venous thrombosis and pulmonary embolism, suggesting that our definition of a VTE study provides a valid estimation of the familial risks.

### Table 5. Familial Standardized Incidence Ratio for Venous Thromboembolism in Siblings by Number of Siblings in Families (Family Size)

<table>
<thead>
<tr>
<th>No. of Siblings (Family Size)</th>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
<td>Observed No. of Cases</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>2 siblings</td>
<td>230</td>
<td>2.47*</td>
<td>1.53*</td>
<td>3.98*</td>
<td>208</td>
<td>2.30*</td>
<td>1.41*</td>
<td>3.73*</td>
<td>438</td>
</tr>
<tr>
<td>3 siblings</td>
<td>361</td>
<td>2.97*</td>
<td>1.89*</td>
<td>4.66*</td>
<td>300</td>
<td>2.49*</td>
<td>1.57*</td>
<td>3.94*</td>
<td>661</td>
</tr>
<tr>
<td>≥4 siblings</td>
<td>661</td>
<td>2.63*</td>
<td>1.72*</td>
<td>4.01*</td>
<td>633</td>
<td>2.49*</td>
<td>1.63*</td>
<td>3.81*</td>
<td>1294</td>
</tr>
<tr>
<td>All</td>
<td>1252</td>
<td>2.69*</td>
<td>1.80*</td>
<td>4.02*</td>
<td>1141</td>
<td>2.37*</td>
<td>1.58*</td>
<td>3.56*</td>
<td>2393</td>
</tr>
</tbody>
</table>

SIR indicates standardized incidence ratio; CI, confidence interval. The risks in males and females were calculated without taking the sex of the probands into account. *95% CI does not include 1.00.
In conclusion, familial factors are important for the development of VTE, at least from the age of 10 to 69 years. The relative contribution of familial factors decreases with age, although the absolute risk increases. Although some sex-related differences exist regarding the age-specific familial incidence rates, familial factors are highly important in both females and males. Our data support the view that VTE is a multifactorial disease with familial risks comparable to those of many other complex disorders. However, in a small fraction of siblings, the familial risk is very high, suggesting a segregation of rare but strong genetic risk factors. Epidemiological studies such as ours may be helpful in designing future genetic studies of VTE.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Venous thromboembolism (VTE) is a major medical health problem. Familial thrombophilia (eg, clustering of VTE) was recognized at the beginning of the 19th century. Like many common human diseases and traits that cluster in families, VTE is considered a complex disorder influenced by several genetic and environmental factors. This nationwide study sought to determine age- and gender-specific familial risks in siblings hospitalized for VTE. Among a total of 45,362 hospitalized cases with VTE, 2393 affected siblings were identified with a familial standardized incidence ratio of 2.45 (95% confidence interval, 1.66 to 3.61). The familial standardized incidence ratios for siblings with 2 and ≥3 affected probands were 51.87 (95% confidence interval, 31.47 to 85.00) and 53.69 (95% confidence interval, 25.59 to 108.50), respectively. Thus, the family history of siblings appears to be an important risk factor for VTE with a higher relative risk than for many identified genetic risk factors. The relative contribution of familial factors decreases with age, although the absolute risk increases. Although some sex-related differences exist regarding the age-specific familial incidence rates, familial factors are highly important in both females and males. In clinical practice, the familial history is an easy accessible risk factor that may be more useful for risk assessment than testing for the presently identified alleles associated with VTE.
Age- and Gender-Specific Familial Risks for Venous Thromboembolism: A Nationwide Epidemiological Study Based on Hospitalizations in Sweden
Bengt Zöller, Xinjun Li, Jan Sundquist and Kristina Sundquist

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