Venous Thromboembolism Does Not Share Strong Familial Susceptibility With Ischemic Stroke
A Nationwide Family Study in Sweden
Bengt Zöller, MD, PhD; Xinjun Li, MD, PhD; Henrik Ohlsson, PhD; Jan Sundquist, MD, PhD; Kristina Sundquist, MD, PhD

Background—Coagulation allelic variants associated with venous thromboembolism (VTE) have been suggested to be involved in the pathogenesis of ischemic stroke. This nationwide study aimed at determining whether VTE shares familial susceptibility with ischemic stroke.

Method and Results—The Swedish Multigeneration Register of 0- to 75-year-old subjects was linked to the Swedish Hospital Discharge Register and the Cause of Death Register for the period 1987 to 2007. Odds ratios (ORs) for VTE and ischemic stroke were determined in 2 ways: odds of ischemic stroke in offspring whose parents had been diagnosed with VTE, and odds of VTE in offspring whose parents had been diagnosed with ischemic stroke. The analyses were repeated for siblings and spouses. Offspring of parents with VTE (n=25 929) were at increased risk for ischemic stroke (n=5595): OR, 1.10 (95% confidence interval [CI], 1.06–1.14). Siblings of probands with VTE (n=45 132) had no increased risk of ischemic stroke (n=1716): OR, 1.05 (95% CI, 1.00–1.11). Spouses of probands with VTE (n=24 106) were at increased risk for ischemic stroke (n=940): OR, 1.18 (95% CI, 1.10–1.27). The risks for VTE in relatives of probands with ischemic stroke were OR, 1.15; 95% CI, 1.10–1.21 (offspring); OR, 1.07; 95% CI, 1.02–1.12 (siblings); and OR, 1.21; 95% CI, 1.11–1.32 (spouses).

Conclusions—VTE does not share strong familial susceptibility with ischemic stroke in the Swedish population. Moreover, familial nongenetic factors contribute to the observed weak familial associations. The present study suggests that it is unlikely that strong shared disease-causing mutations exist to a large extent in the Swedish population. (Circ Cardiovasc Genet. 2011; 4:484-490.)

Key Words: ischemic stroke ♦ family history ♦ thrombosis ♦ risk factors ♦ genetics

Venous thromboembolism (VTE) (venous thrombosis and pulmonary embolism) and thromboembolic arterial diseases (acute myocardial infarction, ischemic 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), whereas 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 of these diseases being separate entities.¹ ² However, this view has, in recent years, been questioned by a number of studies that have found associations between VTE and atherosclerosis and its different thromboembolic manifestations, including ischemic stroke.¹ ⁶

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It has been hypothesized that genetic variants affecting the coagulation system and the risk of VTE also are involved in the pathogenesis of ischemic stroke.⁷ ⁹ However, previous association studies of hemostatic factors and stroke have produced varying results.⁷ ⁹ Some of the available meta-analysis data suggest that factor V Leiden Gln506 (rs6025) and prothrombin G20210A (rs1799963), both important risk factors for VTE, are weak risk factors for ischemic stroke.⁷ ⁸ However, the results of other meta-analysis have not confirmed this.⁹ To determine whether further search for hemostatic variants associated with venous thromboembolism is worthwhile, a clue could come from analysis of families. A key concept in the framework of genetic epidemiology is whether there exists evidence for phenotypic aggregation in families.¹⁰ ¹¹ Clustering of disease is necessary, though not sufficient, to infer a genetic component of a disease.¹⁰ ¹¹ However, the risk of ischemic stroke in patients with a family history of VTE has not been determined. Only 1 case-control study has investigated the link between familial history of

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From the Center for Primary Health Care Research, Region Skåne and Lund University, Malmö, Sweden (B.Z., X.L., H.O., J.S., K.S.); and Stanford Prevention Research Centre, Stanford University School of Medicine, Stanford CA (J.S.).
Correspondence to Bengt Zöller, MD, PhD, Centre for Primary Health Care Research CRC, Floor 11, Bldg 28, Entrance 72, Malmö University Hospital, S-205 02 Malmö, Sweden. E-mail bengt.zoller@med.lu.se
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ischemic stroke and risk of VTE. In that study family history of stroke was a risk factor for idiopathic VTE (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.1).

Family studies have shown that susceptibility to VTE has a heritable basis, transmitted in part by several candidate genes. We hypothesized that the prothrombotic state associated with a family history of VTE might promote ischemic stroke, for example, ischemic stroke, and VTE could share familial susceptibility and cluster in the same families. A novel contribution of the present study is its approach: it was based on a nationwide register of all hospitalizations in Sweden between 1987 and 2007. Use of hospitalized cases eliminated potential selection and recall bias. The Swedish Multigeneration Register (a family dataset) is a validated data source that has been proven to be reliable in the study of numerous familial diseases, including VTE and ischemic stroke.

In this nationwide study, the ORs of ischemic stroke and VTE were determined in 2 ways: risk of ischemic stroke in offspring whose parents had been diagnosed with VTE, and risk of VTE in offspring whose parents had been diagnosed with ischemic stroke. The analyses were repeated for siblings. Moreover, to investigate the contribution of shared environments, spouse effects were assessed. The aim was to determine whether ischemic stroke and VTE share familial susceptibility, that is, cluster in the same families.

**Methods**

We linked several Swedish nationwide population registers, using the unique personal identification number as key. From the Swedish Multigeneration Register we obtained information on family relations (siblings, parents). To be in the register an index person had to be registered in Sweden between January 1, 1961, and December 31, 2007, as well as be born between January 1, 1932, and December 31, 2007. Thus, all offspring are between 0 and 75 years of age. The Swedish Hospital Discharge Register contains complete data for the period since 1987. The Swedish Hospital Discharge Register boasts nearly 90% overall validity. However, the validity for specific cardiovascular disorders such as VTE, myocardial infarction, and stroke is even higher, being around 95%–99. The Swedish mortality register contains all causes of death from 1961–2007. The register of the total population includes, among other information, marital status of the individual as well as country of birth. The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) includes, among other information, educational status of the individual. More than 11.8 million individuals were included in the constructed database. This study was approved by the Ethics Committee of Lund University, Sweden.

**Variable Definition**

VTE patients, classified according to the 9th (1987–1996) and 10th (1997–2007) versions of the International Classification of Diseases (ICD), were identified in the Hospital Discharge Register and the Swedish Cause of Death register. Only main diagnoses were considered to ensure high validity. In agreement with Souto et al., VTE was defined as not only deep venous thrombosis (DVT) and pulmonary embolism (PE), but also superficial venous thrombosis and other forms of venous thrombosis. Thus, VTE was defined as the following ICD-9 and ICD-10 numbers according to Zöllner et al.:

<table>
<thead>
<tr>
<th>ICD-9:</th>
<th>ICD-10:</th>
</tr>
</thead>
<tbody>
<tr>
<td>415G</td>
<td>I10</td>
</tr>
<tr>
<td>416W</td>
<td>I10</td>
</tr>
</tbody>
</table>

Superficial or deep phlebitis or thrombophlebitis (ICD-9: 451 and ICD-10: I80); portal vein thrombosis (ICD-9: 452 and ICD-10: I81); other venous embolism or thrombosis (ICD-9: 453 and ICD-10: I82); cerebral vein thrombosis or cerebral infarction due to cerebral vein thrombosis or arteriovenous malformation (ICD-9: 437 and ICD-10: I16).

VTE indicates venous thromboembolism.

**Table 1. Number of Cases of Ischemic Stroke and Venous Thromboembolism and Share of Fatal Cases**

<table>
<thead>
<tr>
<th>Dataset</th>
<th>VTE, n</th>
<th>Fatal share</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
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<tr>
<td>IV</td>
<td></td>
<td></td>
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<tr>
<td>V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dataset I**

**Cases**

Cases were individuals with VTE (hospitalized or died from stroke during the period 1987–2007) who had at least 1 sibling living in Sweden sometime between 1987 and 2007.

**Control Subjects**

Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s VTE, and not hospitalized for VTE during the period 1987–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and having a sibling living in Sweden sometime during the period 1987–2007.
Exposure
Exposure was considered if 1 or more of the siblings had been hospitalized or died of stroke.

Dataset II
Cases
Cases were individuals with stroke (hospitalized or died of stroke during the period 1987–2007) who had at least 1 sibling living in Sweden some time between 1987 and 2007.

Control Subjects
Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s stroke, and not hospitalized for stroke during the period 1987–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and having a sibling living in Sweden sometime during the period 1987–2007.

Exposure
Exposure was considered if 1 or more of the siblings had been hospitalized or died of VTE.

Dataset III
Cases
Cases were individuals with VTE (hospitalized or died from stroke during the period 1987–2007) who had both parents living in Sweden sometime between 1987 and 2007.

Control Subjects
Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s VTE, and not hospitalized for VTE during the period 1987–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and having both parents living in Sweden some time during the period 1987–2007.

Table 2. Descriptive Statistics of Individuals With VTE/Stroke During the Period 1987–2007 and Results From the Conditional Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Dataset I</th>
<th>VTE, n</th>
<th>Mean Age for VTE, y (SD)</th>
<th>Stroke Among Siblings to Cases</th>
<th>Control Subjects, n</th>
<th>Stroke Among Siblings to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>45 132</td>
<td>49 (14)</td>
<td>1716 (3.80%)</td>
<td>225 660</td>
<td>8174 (3.62%)</td>
<td>1.05 (1.00–1.11)</td>
</tr>
<tr>
<td>Men</td>
<td>21 914</td>
<td>51 (13)</td>
<td>864 (3.94%)</td>
<td>109 570</td>
<td>4246 (3.88%)</td>
<td>1.02 (0.95–1.10)</td>
</tr>
<tr>
<td>Women</td>
<td>23 218</td>
<td>47 (15)</td>
<td>852 (3.67%)</td>
<td>116 090</td>
<td>3928 (3.38%)</td>
<td>1.09 (1.01–1.18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dataset II</th>
<th>Stroke, n</th>
<th>Mean Age for Stroke, y (SD)</th>
<th>VTE Among Siblings to Cases</th>
<th>Control Subjects, n</th>
<th>VTE Among Siblings to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>60 549</td>
<td>56 (11)</td>
<td>2400 (3.96%)</td>
<td>302 745</td>
<td>10 457 (3.45%)</td>
<td>1.15 (1.10–1.21)</td>
</tr>
<tr>
<td>Men</td>
<td>37 013</td>
<td>56 (10)</td>
<td>1431 (3.87%)</td>
<td>185 065</td>
<td>6385 (3.45%)</td>
<td>1.12 (1.06–1.19)</td>
</tr>
<tr>
<td>Women</td>
<td>23 536</td>
<td>56 (12)</td>
<td>969 (4.12%)</td>
<td>117 680</td>
<td>4072 (3.46%)</td>
<td>1.20 (1.12–1.29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dataset III</th>
<th>VTE, n</th>
<th>Mean Age for VTE, y (SD)</th>
<th>Stroke Among Parents to Cases</th>
<th>Control Subjects, n</th>
<th>Stroke Among Parents to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>25 929</td>
<td>42 (13)</td>
<td>5595 (21.58%)</td>
<td>129 645</td>
<td>26 118 (20.15%)</td>
<td>1.10 (1.06–1.14)</td>
</tr>
<tr>
<td>Men</td>
<td>12 001</td>
<td>45 (12)</td>
<td>2863 (23.86%)</td>
<td>60 005</td>
<td>13 367 (22.28%)</td>
<td>1.10 (1.05–1.15)</td>
</tr>
<tr>
<td>Women</td>
<td>13 928</td>
<td>40 (13)</td>
<td>2732 (19.62%)</td>
<td>69 640</td>
<td>12 751 (18.31%)</td>
<td>1.10 (1.05–1.15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dataset IV</th>
<th>Stroke, n</th>
<th>Mean Age for Stroke, y (SD)</th>
<th>VTE Among Parents to Cases</th>
<th>Control Subjects, n</th>
<th>VTE Among Parents to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>22 525</td>
<td>49 (11)</td>
<td>2188 (9.71%)</td>
<td>112 625</td>
<td>10 296 (9.14%)</td>
<td>1.07 (1.02–1.12)</td>
</tr>
<tr>
<td>Men</td>
<td>14 289</td>
<td>50 (10)</td>
<td>1366 (9.56%)</td>
<td>71 445</td>
<td>6629 (9.28%)</td>
<td>1.03 (0.97–1.10)</td>
</tr>
<tr>
<td>Women</td>
<td>8236</td>
<td>48 (11)</td>
<td>822 (9.98%)</td>
<td>41 180</td>
<td>3667 (8.90%)</td>
<td>1.14 (1.05–1.23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dataset V</th>
<th>VTE, n</th>
<th>Mean Age for VTE, y (SD)</th>
<th>Stroke Among Spouses to Cases</th>
<th>Control Subjects, n</th>
<th>Stroke Among Spouses to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24 106</td>
<td>55 (11)</td>
<td>940 (3.90%)</td>
<td>120 530</td>
<td>4015 (3.33%)</td>
<td>1.18 (1.10–1.27)</td>
</tr>
<tr>
<td>Men</td>
<td>12 109</td>
<td>57 (9)</td>
<td>266 (2.20%)</td>
<td>60 545</td>
<td>1107 (1.83%)</td>
<td>1.21 (1.05–1.38)</td>
</tr>
<tr>
<td>Women</td>
<td>11 992</td>
<td>53 (11)</td>
<td>672 (5.60%)</td>
<td>59 960</td>
<td>2908 (4.85%)</td>
<td>1.17 (1.07–1.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dataset VI</th>
<th>Stroke, n</th>
<th>Mean Age for Stroke, y (SD)</th>
<th>VTE Among Spouses to Cases</th>
<th>Control Subjects, n</th>
<th>VTE Among Spouses to Control Individuals</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>31 925</td>
<td>59 (8)</td>
<td>682 (2.14%)</td>
<td>159 625</td>
<td>2833 (1.77%)</td>
<td>1.21 (1.11–1.32)</td>
</tr>
<tr>
<td>Men</td>
<td>20 793</td>
<td>60 (8)</td>
<td>382 (1.84%)</td>
<td>103 965</td>
<td>1548 (1.49%)</td>
<td>1.24 (1.11–1.39)</td>
</tr>
<tr>
<td>Women</td>
<td>11 126</td>
<td>59 (9)</td>
<td>300 (2.70%)</td>
<td>55 630</td>
<td>1285 (2.31%)</td>
<td>1.17 (1.03–1.33)</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism.
Exposure
Exposure was considered if either of the parents had been hospitalized or died of stroke.

Dataset IV

Cases
Cases were individuals with stroke (hospitalized or died of stroke during the period 1987–2007) who had at least 1 parent living in Sweden sometime between 1987 and 2007.

Control Subjects
Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s stroke, and not hospitalized for stroke during the period 1987–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and having both parents living in Sweden sometime during the period 1987–2007.

Exposure
Exposure was considered if either of the parents had been hospitalized or died of VTE.

Dataset V

Cases
Cases were individuals with VTE (hospitalized or died of stroke during the period 1991–2007) who were married the year before the VTE diagnosis.

Control Subjects
Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s VTE, and not hospitalized for VTE during the period 1991–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and married during the same year as the case.

Exposure
Exposure was considered if the spouse had been hospitalized or died of stroke.

Dataset VI

Cases
Cases were individuals with stroke (hospitalized or died of stroke during the period 1991–2007) who were married the year before the stroke diagnosis.

Control Subjects
Five control subjects were chosen randomly among individuals who were alive, living in Sweden at the time of the case’s stroke, and not hospitalized for stroke during the period 1991–2007. Control subjects were matched to cases based on age, sex, country of birth, education (measured the year before the date of diagnosis), and married during the same year as the case.

Exposure
Exposure was considered if the spouse had been hospitalized or died of VTE.

The matching procedure has been successfully used in previous studies, as described by Lichtenstein et al. We used conditional logistic regression to investigate the difference in exposure between cases and control subjects as described by Lichtenstein et al. We present ORs and a corresponding 95% CI. All calculations were performed using SAS version 9.2.

Results
Table 1 presents the number of identified cases of VTE and ischemic stroke for sibling analysis, parent-offspring analysis, and spouse analysis. The majority of cases were hospitalized. Only a small proportion involved fatal cases (Table 1).

In both male and female offspring whose parent had been diagnosed with VTE, a slightly increased risk of ischemic stroke was observed (Table 2 and Figure 1). Among siblings, only women had a significantly increased risk of ischemic stroke.

In female offspring whose parent had been diagnosed with ischemic stroke, a slightly increased risk of VTE was observed (Table 2 and Figure 2). Among siblings, both men and women had a significantly increased risk of VTE.

To investigate the nongenetic, familial environmental contribution, the spouse effect was assessed (Table 2). An
increased risk of ischemic stroke was observed in both men and women whose spouses had been diagnosed with VTE (Table 2). Similar increased risks of VTE were observed in both men and women whose spouses had been diagnosed with VTE.

Discussion

To our knowledge, this is the first nationwide attempt to assess whether ischemic stroke and VTE share familial susceptibility. Only weak familial associations between VTE and ischemic stroke were observed among siblings and parent-offspring. Similar associations were observed among spouses, suggesting a familial nongenetic contribution to the observed associations. These findings suggest that no strong shared disease-causing mutation exist to a large extent in the Swedish population.

It seems paradoxical that the hypercoagulable state associated with familial history of VTE13–17 is not a strong risk factor for ischemic stroke. However, arterial (ischemic stroke) and venous (VTE) diseases differ significantly in terms of epidemiology and pathophysiology.1–6 Moreover, it is an old observation that injection of thrombin in dogs under certain condition has an anticoagulant effect and might even induce a bleeding diathesis.27 This is due to binding of thrombin to thrombomodulin and activation of protein C.28 Thus, an increased thrombin generation, which is described among patients with familial thrombophilia,29 could under certain conditions through binding to thrombomodulin even have anticoagulant effects.27,28 It is therefore possible that a slight increased thrombin generation due to mild venous thrombophilia might be balanced by its anticoagulant effect. In fact, increased F1 + 2 (prothrombin activation fragment) and TAT (thrombin-antithrombin complex), which are markers of coagulation activation, were not risk factors for coronary heart disease or stroke in a prospective study.30

Only 1 other article has studied the relationship between family history of stroke and risk of VTE.12 In that study, which was smaller than the present one, an association (adjusted OR, 1.5; 95% CI, 1.1–2.1) was observed but only for family history of stroke in idiopathic VTE patients, that is, VTE without major provoking factors.12 The reverse association was not studied, that is, risk of stroke when family history of VTE was present. In the present study, it was not possible to separate idiopathic cases from nonidiopathic ones. However, the present study, a nationwide investigation, was larger than previous research. We also separated ischemic stroke from hemorrhagic stroke. Moreover, the present model has been shown to be reliable for studying familial risks26 and is not affected by recall bias to cases or relatives. Another difference is that the previous study focused on deep venous thrombosis and pulmonary embolism, whereas the present one included all VTE manifestations. However, no indications of familial heterogeneity among the different VTE manifestations included in the present study could be demonstrated.16 Even rare forms of VTE have a familial background.31

Because no strong risk for stroke among relatives to probands with VTE was observed in our study, it is unlikely that any shared strong genetic risk factors exist between ischemic stroke and VTE. In addition, meta-analysis have found only weak or no associations between factor V Leiden Gln506 (rs6025) and prothrombin G20210A (rs1799963), both important risk factors for VTE and ischemic stroke.7–9 In fact, genome-wide association studies (GWAS) of stroke have not to date identified any genetic variants that are associated with venous thrombophilia.32 GWAS of stroke have been performed in 6 cohorts, yielding 8 publications with somewhat inconsistent results.32 No single locus has yet been identified in 2 independent stroke GWAS at a genomewide level of significance. However, these negative results may be related to the study design and stringency of GWAS.33 More recent approaches such as PheWAS might uncover genetic connections between stroke and venous thromboembolism.33 However, factor V Leiden (rs6025) has been confirmed to be a VTE risk factor in a genome-wide analysis of VTE.34 The findings of the present epidemiological study that no strong association exists between familial ischemic stroke and VTE confirms the results of GWAS that still have not found any common genetic variant for VTE and ischemic stroke,32,34 thus, the observed increased risk of ischemic stroke and atherosclerosis among VTE patients may not be due to familial genetic factors.1–5 Instead, it may be more likely that acquired factors are involved rather than a shared heritable susceptibility.

The present study has a number of advantages. These include complete nationwide coverage in a country of high medical standards and medical diagnosis of patients by specialists during extended examinations in clinics. In addition, the results were not affected by recall bias because both the probands and cases were medically diagnosed. Importantly, the Multigeneration Register is a validated source that has been proved to be reliable in the study of many familial diseases.16,18–21,28 Data in the MigMed 2 database are almost complete.

The present study has also a number of limitations. (1) The Swedish Hospital Discharge Register contains complete data only for the period since 1987. (2) Another potential limitation is that we do not have access to the methods used for objective diagnoses. (3) A further limitation is that only hospitalized and fatal patients were included; outpatient data were unavailable. (4) Another possible limitation is that our data do not include risk factors for VTE or stroke, which is a potential confounder. However, these limitations were addressed as follows: (1) We thus chose the 21-year period between 1987 and the present study that covered a period of 21 years. Events that occurred before 1987 are unknown, which probably creates a nondifferential bias regarding familial risks estimates; for example, familial and nonfamilial VTE or stroke cases diagnosed before are most likely lost in proportion to familial risks. (2) The register has high validity, especially for cardiovascular disorders such as VTE, stroke, and myocardial infarction being around 95%.22–24 (3) The loss of outpatients is most likely only a source of nondifferential error regarding the estimation of familial risks. Stroke patients are rarely treated as outpatients in Sweden. Moreover, in Sweden, almost all cases of pulmonary embolism
are treated at hospitals, and the number of cases of hospital-treated pulmonary embolism have been virtually constant from 1987 to 1998. However, regarding hospital treatment of DVT in Sweden, a reduction in the number of cases was observed between 1987 and 1998. In 1998, 50% of DVT patients in Sweden were treated directly as outpatients. As a compromise, cases and control subjects were matched for educational level, which is related to many risk factors for VTE and stroke.

Conclusions

The present study demonstrates that venous thromboembolism does not share strong familial susceptibility with ischemic stroke in the Swedish population. It seems unlikely that strong shared disease-causing mutations exist to a large extent in the Swedish population. Familial nongenetic environmental factors may rather contribute to the observed familial associations. Whether our findings are valid in other populations remains to be determined.

Acknowledgments

The registers used in the present study are maintained at Statistics Sweden and the National Board of Health and Welfare.

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Disclosures

None.

References


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CLINICAL PERSPECTIVE

Allelic variants associated with venous thromboembolism (VTE) have been suggested to be involved in the pathogenesis of ischemic stroke. We hypothesized that the prothrombotic state associated with a family history of VTE might promote ischemic stroke, that is, that ischemic stroke and VTE cluster in the same families. In this nationwide study, the odds ratios (ORs) of ischemic stroke and VTE were determined in 2 ways: (1) odds of ischemic stroke in offspring whose parents had been diagnosed with VTE and (2) odds of VTE in offspring whose parents had been diagnosed with ischemic stroke. The analyses were repeated for siblings and spouses to investigate the contribution of shared family environments. Offspring of parents with VTE (n=25 929) had slightly increased odds of ischemic stroke (n=5595): OR, 1.10 (95% confidence interval, 1.06–1.14). Siblings of probands with VTE (n=45 132) had no increased risk of ischemic stroke (n=1716): OR, 1.05 (95% confidence interval, 1.00–1.11). Spouses of probands with VTE (n=24 106) had increased odds of ischemic stroke (n=940): OR, 1.18 (95% confidence interval, 1.10–1.27). Similarly, the odds of VTE in relatives of probands with ischemic stroke were slightly/moderately increased. VTE does not share strong familial susceptibility with ischemic stroke in the Swedish population.
Venous Thromboembolism Does Not Share Strong Familial Susceptibility With Ischemic Stroke: A Nationwide Family Study in Sweden
Bengt Zöller, Xinjun Li, Henrik Ohlsson, Jan Sundquist and Kristina Sundquist

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