Venous Thromboembolism Does Not Share Strong Familial Susceptibility
With Ischemic Stroke: A Nationwide Family Study in Sweden

Running title: Zöller et al.; Familial venous thromboembolism and stroke

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Abstract:

**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 0-75-year-old subjects was linked to the Swedish Hospital Discharge Register and the Cause of Death Register for the period 1987-2007. Odds ratios (OR), for VTE, and ischemic stroke were determined in two 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 1.18 (95% CI 1.10-1.27). Siblings of probands with VTE (n=45,132) had no increased risk of ischemic stroke (n=17,16): 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** - Venous thromboembolism does not share strong familial susceptibility with ischemic stroke in the Swedish population. Moreover, familial non-genetic 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.

**Key words:** ischemic stroke, family history, thrombosis, risk factors, genetics
Introduction

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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{1-6}

It has been hypothesised that genetic variants affecting the coagulation system and the risk of VTE also are involved in the pathogenesis of ischemic stroke.\textsuperscript{7-9} However, previous association studies of haemostatic factors and stroke have produced varying results.\textsuperscript{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.\textsuperscript{7,8} However, the results of other meta-analysis have not confirmed this.\textsuperscript{9} To determine whether further search for haemostatic 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.\textsuperscript{10-11} Clustering of disease is necessary, though not sufficient, to infer a genetic component of a disease.\textsuperscript{10-11} However, the risk of ischemic stroke in patients with a family history of VTE has not been determined. Only one case-control study has investigated the link between familial history of ischemic stroke and risk of VTE.\textsuperscript{12} In that study family history of stroke was a risk factor for idiopathic VTE (OR 1.5, 95% CI 1.1-2.1).
Family studies have shown that susceptibility to VTE has a heritable basis,\(^{13-16}\) transmitted in part by several candidate genes.\(^{13,17}\) We hypothesised that the prothrombotic state associated with a family history of VTE\(^{13-16}\) might promote ischemic stroke, i.e. 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 hospitalisations in Sweden between 1987 and 2007. Use of hospitalised 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.\(^{16,18-21}\)

In this nationwide study, the odds ratios (OR), of ischemic stroke and VTE was determined in two 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, i.e. 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 Jan 1, 1961 and Dec 31 2007 as well as be born between Jan 1, 1932 and Dec 31, 2007. Thus, all offspring are between 0-75 years. 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%. The Swedish mortality register contains all causes of death from 1961 to 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. Over 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 ninth (1987–1996) and tenth (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 (SVT) and other forms of venous thrombosis. Thus, VTE was defined as the following ICD-9 and ICD-10 numbers according to Zöller et al.: PE (ICD-9: 415B, 416W and ICD-10: I26); 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 (ICD-9: 437G and ICD-10: I636, I676); pregnancy-related venous thromboembolism (ICD-9: 671C. 671D, 671E, 671F, 671X, 673C and ICD-10: O222, O223, O225, O228, O229, O870, O871, O873, O879 and O882); and abortion-related venous thromboembolism (ICD-9: 639G and ICD-10: O082, O087). Ischemic stroke was defined as...

For each degree of relatedness (sibling, parent, spouse) we created separate datasets. In total we analyzed six different datasets. (see table 1 and 2 for the descriptive statistics for the different subsets used in the analysis):

I. Cases: Individuals with VTE (hospitalized or died from stroke during the period 1987-2007) who had at least one sibling living in Sweden sometime between 1987 and 2007.

Controls: Five controls 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. Controls were matched to cases based on age, gender, 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: If one or more of the siblings had been hospitalized or died from stroke.

II. Cases: Individuals with stroke (hospitalized or died from stroke during the period 1987-2007) who had at least one sibling living in Sweden sometime between 1987 and 2007.

Controls: Five controls 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. Controls were matched to cases based on age, gender, 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: If one or more of the siblings had been hospitalized or died from VTE.

III. Cases: 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.

Controls: Five controls 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. Controls were matched to cases based on age, gender, 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:* If either of the parents had been hospitalized or died from stroke.

**IV. Cases:** Individuals with stroke (hospitalized or died from stroke during the period 1987-2007) who had at least one parent living in Sweden sometime between 1987 and 2007.

*Controls:* Five controls 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. Controls were matched to cases based on age, gender, 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:* If either of the parents had been hospitalized or died from VTE.

**V. Cases:** Individuals with VTE (hospitalized or died from stroke during the period 1991-2007) who were married the year prior to the VTE diagnosis.

*Controls:* Five controls 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. Controls were matched to cases based on age, gender, country of birth, education (measured the year before the date of diagnosis) and married during the same year as the case.

*Exposure:* If the spouse had been hospitalized or died from stroke.

**VI. Cases:** Individuals with stroke (hospitalized or died from stroke during the period 1991-2007) who were married the year prior to the stroke diagnosis.

*Controls:* Five controls 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. Controls were matched to cases based on age, gender, country of birth, education (measured the year before the date of diagnosis) and married during the same year as the case.

**Exposure**: If the spouse had been hospitalized or died from VTE.

The matching procedure has been successfully employed in previous studies, as described by Lichtenstein et al.\(^26\) We used conditional logistic regression to investigate the difference in exposure between cases and controls as described by Lichtenstein et al.\(^26\) We present odds ratios (ORs) and a corresponding 95% confidence interval. 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 was 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 both male and 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 non-genetic, familial environmental contribution, the spouse effect was assessed (Table 2). An increased risk of ischemic stroke was observed in both males and females whose spouses had been diagnosed with VTE (Table 2). Similar increased risks of
VTE were observed in both males and females 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 non-genetic 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 VTE,\textsuperscript{13-17} 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.\textsuperscript{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.\textsuperscript{27} This is due to binding of thrombin to thrombomodulin and activation of protein C.\textsuperscript{28} Thus, an increased thrombin generation, which is described among patients with familial thrombophilia,\textsuperscript{29} could under certain conditions through binding to thrombomodulin even have anticoagulant effects.\textsuperscript{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.\textsuperscript{30}

Only one other article has studied the relationship between family history of stroke and
risk of VTE. In that study, which was smaller than the present one, an association (adjusted odds ratio 1.5, 95% CI 1.1-2.1) was observed but only for family history of stroke in idiopathic VTE patients, i.e. VTE without major provoking factors. The reverse association was not studied, i.e. risk of stroke when family history of VTE was present. In the present study, it was not possible to separate idiopathic cases from non-idiopathic ones. However, the present study, a nationwide investigation, was larger than previous research. We also separated ischemic stroke from haemorrhagic stroke. Moreover, the present model has been shown to be reliable for studying familial risks, 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, while 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. Even rare forms of VTE have a familial background.

As 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. In fact, genome-wide association studies (GWASs) of stroke have not to date identified any genetic variants that are associated with venous thrombophilia. GWASs of stroke have been performed in six cohorts, yielding eight publications with somewhat inconsistent results. No single locus has yet been identified in two independent stroke GWASs at a genome-wide level of significance. However, these negative results may be related to the study design and stringency of GWAS. More recent approaches such as PheWAS might uncover genetic connections between stroke and venous
thromboembolism. However, factor V Leiden (rs6025) has been confirmed to be a VTE risk factor in a genome-wide analysis of VTE. The findings of the present epidemiological study that no strong association exists between familial ischemic stroke and VTE confirms the results of genome-wide association studies that still have not found any common genetic variant for VTE and ischemic stroke. Thus, the observed increased risk of ischemic stroke and atherosclerosis among VTE patients may not be due to familial genetic factors. 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 diagnoses 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. 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 hospitalised and fatal patients were included; outpatient data was 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 most likely creates a non-differential bias regarding familial risks estimates, i.e. familial and non-familial 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 non-differential 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,35 and the number of cases of hospital-treated pulmonary embolism have been virtually constant from 1987-1998.35 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.35 4) As a compromise, cases and controls 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 non-genetic environmental factors may rather contribute to the observed familial associations. Whether our findings are valid in other populations remains to be determined.

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

Funding Sources: This work was supported by grants to Drs Kristina and Jan Sundquist from the Swedish Research Council (2008-3110 and 2008-2638), the Swedish Council for Working Life and Social Research (2006-0386, 2007-1754 and 2007-1962 ) and the Swedish Research Council Formas (2006-4255-6596-99 and 2007-1352), and to Bengt Zöller from Region Skåne (124611).

Conflict of Interest Disclosures: None.
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Table 1: Number of cases of ischemic stroke and venous thromboembolism and share of fatal cases

<table>
<thead>
<tr>
<th></th>
<th>VTE (n)</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sibling analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dataset I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>45 132</td>
<td>879 (1.95%)</td>
</tr>
<tr>
<td>Men</td>
<td>21 914</td>
<td>492 (2.25 %)</td>
</tr>
<tr>
<td>Women</td>
<td>23 218</td>
<td>387 (1.67%)</td>
</tr>
<tr>
<td>Dataset II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>60 549</td>
<td>589 (1.00%)</td>
</tr>
<tr>
<td>Men</td>
<td>37 013</td>
<td>330 (0.89%)</td>
</tr>
<tr>
<td>Women</td>
<td>23 536</td>
<td>259 (1.29%)</td>
</tr>
<tr>
<td><strong>Parent analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dataset III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>25 929</td>
<td>376 (1.45%)</td>
</tr>
<tr>
<td>Men</td>
<td>12 001</td>
<td>219 (1.82%)</td>
</tr>
<tr>
<td>Women</td>
<td>13 928</td>
<td>157 (1.13%)</td>
</tr>
<tr>
<td>Dataset IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>22 525</td>
<td>175 (0.78%)</td>
</tr>
<tr>
<td>Men</td>
<td>14 289</td>
<td>107 (0.75%)</td>
</tr>
<tr>
<td>Women</td>
<td>8 236</td>
<td>68 (0.83%)</td>
</tr>
<tr>
<td><strong>Spouse analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dataset V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>24 106</td>
<td>417 (1.70%)</td>
</tr>
<tr>
<td>Men</td>
<td>12 109</td>
<td>214 (1.77%)</td>
</tr>
<tr>
<td>Women</td>
<td>11 992</td>
<td>197 (1.64%)</td>
</tr>
<tr>
<td>Dataset VI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>31 925</td>
<td>274 (0.86%)</td>
</tr>
<tr>
<td>Men</td>
<td>20 793</td>
<td>154 (0.74 %)</td>
</tr>
<tr>
<td>Women</td>
<td>11 126</td>
<td>120 (1.08 %)</td>
</tr>
</tbody>
</table>
**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 (SD)</th>
<th>Stroke among siblings to cases</th>
<th>Controls (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>1 716 (3.80 %)</td>
<td>225 660</td>
<td>8 174 (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>4 246 (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>3 928 (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 (SD)</th>
<th>VTE among siblings to cases</th>
<th>Controls (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>2 400 (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>1 431 (3.87 %)</td>
<td>185 065</td>
<td>6 385 (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>4 072 (3.46 %)</td>
<td>1.20 (1.12–1.29)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Dataset III</th>
<th>VTE (n)</th>
<th>Mean age for VTE (SD)</th>
<th>Stroke among parents to cases</th>
<th>Controls (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>5 595 (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>2 863 (23.86 %)</td>
<td>80 005</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>2 732 (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 (SD)</th>
<th>VTE among parents to cases</th>
<th>Controls (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>2 188 (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>1 366 (9.56 %)</td>
<td>71 445</td>
<td>6 629 (9.28 %)</td>
<td>1.03 (0.97–1.10)</td>
</tr>
<tr>
<td>Women</td>
<td>8 236</td>
<td>48 (11)</td>
<td>822 (9.98 %)</td>
<td>41 180</td>
<td>3 667 (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 (SD)</th>
<th>Stroke among spouses to cases</th>
<th>Controls (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>4 015 (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>1 107 (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>2 908 (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 (SD)</th>
<th>VTE among spouses to cases</th>
<th>Controls (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>2 833 (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>1 548 (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>1 285 (2.31 %)</td>
<td>1.17 (1.03–1.33)</td>
</tr>
</tbody>
</table>
**Figure Legends:**

Figure 1. Forest plot showing the risk of stroke among relatives to individuals with VTE compared to control individuals.

Figure 2. Forest plot showing the risk of VTE among relatives to individuals with stroke compared to control individuals.
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

Circ Cardiovasc Genet. published online August 31, 2011;
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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