ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Venous Thromboembolism and Varicose Veins Share Familial Susceptibility: A Nationwide Family Study in Sweden

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***Background*—**Varicose veins (VVs) have been associated with venous thromboembolism (VTE), but whether these diseases share familial susceptibility has not been determined. This nationwide study aimed to determine whether VTE shares familial susceptibility with VVs.

***Methods and Results*—**Swedish Multigeneration Register data for persons aged 0 to 76 years during the period 1964–2008 were linked to the Swedish Inpatient and Outpatient Registers. Familial risks (standardized incidence ratios [SIRs]) of VTE and VVs were examined in 2 ways (ie, bidirectionally): risk of VTE in subjects whose siblings had been diagnosed with VVs and risk of VVs in persons whose siblings had been diagnosed with VTE. The analyses were repeated for spouses to determine the importance of shared adult family environment. In total, 96 810 siblings had VVs and 87 564 had VTE. An increased risk of VTE was observed in persons whose siblings had VVs (SIR 1.30, 95% CI 1.26 to 1.33), whereas persons whose siblings had VTE had an increased risk of VVs (SIR 1.30, 95% CI 1.27 to 1.34). If 2 or more siblings were affected by VTE, the risk for VVs was 1.70 (95% CI 1.53 to 1.88). Conversely, if 2 or more siblings were affected by VVs, the risk for VTE was 1.52 (95% CI 1.38 to 1.67). In spouses of VTE patients, a minor increased risk of VVs was observed (SIR 1.05 for husbands, SIR 1.06 for wives). The risk of VTE in spouses of VV patients was similarly small (SIR 1.01 for husbands, SIR 1.05 for wives).

***Conclusions*—**VVs and VTE share familial susceptibility. This novel finding suggests the existence of shared familial and possibly genetic factors. **(*J Am Heart Assoc*. 2014;3:e000850 doi: 10.1161/JAHA.114.000850)**

Key Words: embolism • epidemiology • genetics • thrombosis • veins

Venous thromboembolism (VTE) is a major cardiovascular disease.[1–6] A number of inherited and acquired risk factors for VTE have been described.[1–6] These include advancing age, malignancy, pregnancy, oral contraceptive use, hormone replacement therapy, surgery, immobilization, obesity, and inherited thrombophilia. Varicose veins (VVs) have also been indicated as risk factor for VTE.[7,8]

Family studies have shown that susceptibility to VTE has a heritable basis, with familial risks of ≈2 to 3.[9–19] Several genetic risk factors have been implicated in the familial aggregation of VTE (familial thrombophilia), the 5 strongest of which are factor V Leiden (rs6025), prothrombin G20210A (rs1799963), and deficiencies of the natural anticoagulants antithrombin, protein C, and protein S.[1,12] VVs have also been shown to aggregate in families.[20–25] No genomewide association study has yet been performed in patients with VVs. In a candidate gene study, however, a mutation in the thrombomodulin gene promoter was associated with VVs.[26] An increased prevalence of familial thrombophilia among patients with VVs or venous ulcers has also been suggested.[27–31] Familial thrombophilia has also been associated with superficial thrombophlebitis (thrombosis of the superficial veins).[32,33] Consequently, a number of links exist between VVs and familial thrombophilia; however, whether family history of VVs is a risk factor for VTE has not been determined. In addition, the risk of VVs in patients with a family history of VTE has not been determined. Familial aggregation is necessary, but not sufficient, to infer a genetic cause.[34,35] Both genetic and nongenetic factors might contribute to increased familial aggregation.[34,35]

The aim of the present study was to determine whether VVs and VTE share familial susceptibility. We hypothesized that familial aggregation of VVs is associated with VTE and that family history of VTE might promote VVs. In a nationwide family study, familial risk of VVs and VTE was analyzed in 2

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ways (ie, bidirectionally): risk of VTE in subjects whose siblings had been diagnosed with VVs and risk of VVs in subjects whose siblings had been diagnosed with VTE. To investigate the contribution of adult shared family environment, spouses' risks were assessed.

Methods

This study was approved by the ethics committee of Lund University, Sweden. Data used in this study represented information on all persons registered as residents of Sweden. It included individual-level information on age, sex, education, siblings, spouses, socioeconomic status (occupation), geographic region of residence, hospital and outpatient diagnoses, dates of hospital admissions (1964–2008), date of emigration, and date and cause of death. The data sources comprised several national Swedish registers, including the Swedish National Population and Housing Census (1960–1990), the Total Population Register, the Immigration Register, the Multigeneration Register, the Swedish Hospital Discharge Register (1964–2008), and the Outpatient Register (2001–2008), provided to us by Statistics Sweden (a Swedish government–owned statistics bureau) and the National Board of Health and Welfare.[14–19,36–39]

Statistics Sweden provided the Multigeneration Register, in which persons born in Sweden since 1932 are linked to their siblings. Data were linked to national census data to retrieve information relating to individual-level socioeconomic status and, finally, to data from the Swedish Hospital Discharge Register and Outpatient Register. Data linkage was performed using the personal identification numbers that are assigned to all residents in Sweden for their lifetimes. For each person, this number was replaced by a serial number to maintain anonymity. The serial number was used to check that each person was entered only once for his or her first VTE or VV diagnosis (as a cause of hospitalization). The follow-up time ran from January 1, 1964, until December 31, 2008.

Data in the Swedish registers are remarkably complete. In 2001, personal identification numbers were missing for only 0.4% of hospitalizations, and main diagnosis was missing for 0.9% of hospitalizations.[37] Information on occupational status, retrieved from national census records, was 99.2% complete.[37] The Swedish Hospital Discharge Register was started in 1964 and has had nationwide coverage since 1987. It boasts nearly 90% overall validity.[36,38,39] Validity for specific cardiovascular disorders such as VTE, myocardial infarction, and stroke is even higher (around 95%).[36,38–41]

Outcome Variable

Patients with VTE and VVs, classified according to different revisions of the World Health Organization International Classification of Diseases (ICD; ICD-7 before 1968, ICD-8 from 1968 to 1986, ICD-9 from 1987 to 1996, and ICD-10 from 1997 onward), were identified in the Hospital Discharge Register and the Outpatient Register. Only main diagnoses of VTE and VVs were considered to ensure high validity. VTE was defined by the following ICD codes, as previously described:[14–19] 463, 464, 465, 466, 583.00, 334.40, 334.50, 682, and 684 (ICD-7); 450, 451, 452, 453, 671, and 673.9 (ICD-8); 437G, 451, 452, 453, 415B, 416W, 671C, 671D, 671E, 671F, 671X, 673C, and 639G (ICD-9); and I26, I636, I676, I80, I81, I82, O222, O223, O225, O228, O229, O870, O871, O873, O879, O882, O082, and O087 (ICD-10). VTE was further subjected to subanalyses of venous thrombosis of the legs, pulmonary embolism, and other forms of venous thromboembolism (Table 1).

VVs were defined by the following ICD codes:[25] 460 (ICD-7), 454 (ICD-8), 454 and 671A (ICD-9), and I83 and O220 (ICD-10). Individuals diagnosed with VVs during the follow-up period were identified based on their first recorded diagnosis in the Hospital Discharge Register or Outpatient Register. Uncomplicated VVs (no inflammation or ulceration) were defined by the following ICD codes: 460.00 and 460.10 (ICD-7), 454.99 (ICD-8), 454X and 671A (ICD-9), and I83.9 and O22.0 (varicose veins during pregnancy) (ICD-10). Complicated varicose veins (with ulceration and/or inflammation) were defined by the following ICD codes: 460.20 (varicose veins with ulcer) (ICD-7); 454.00 (varicose veins with ulcer (ICD-8); 454A (varicose veins with ulcer), 454B (varicose veins with inflammation), and 454C (varicose veins with ulcer and inflammation) (ICD-9); and I83.0 (varicose veins with ulcer),

Table 1. ICD Codes for the Different Subtypes of VTE

	ICD-7	ICD-8	ICD-9	ICD-10
VT	463, 682.00	451, 671	451, 671C, 671D, 671E, 671X	I80, O222, O223, O228, O229, O870, O871, O879, O087
PE	405, 684	450, 673.9	415B, 416W, 673C, 639G	I26, O882, O082
OVTE	334.40, 334.50, 464, 466, 583.00, 682.10, 682.99	452, 453	452, 453, 437G, 671F	I81, I82, I636, I676, O225, O873

ICD indicates International Classification of Diseases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; VT, venous thrombosis of the legs.

I83.1 (varicose veins with inflammation), and I83.2 (varicose veins with ulcer and inflammation) (ICD-10).

Predictor Variable

The predictor variable was diagnosis of VTE or VVs during the study period (1964–2008) for a sibling, namely, a sibling history of VTE or VVs, respectively. To analyze the effect of shared household in adulthood, the risk of VTE or VVs in spouses were analyzed in those with a spouse affected by VVs or VTE, respectively. Spouses were defined on the basis of common children born 1932 or later.

Adjustment Variables

Adjustments were made for sex, age, time period, socioeconomic status, and geographic region of residence. Sex was male or female. Age was age at diagnosis (5-year age group categories). Time period was the time divided into 4 different follow-up periods (1965–1974, 1975–1984,

Table 2. Basic Characteristics in Patients With VVs and VTE

Basic Characteristics	VVs		VTE	
	n	%	n	%
Sex				
Male	28 336	29.3	41 456	47.3
Female	68 474	70.7	46 108	52.7
Age, y				
<30	7232	7.5	10 599	12.1
30 to 39	22 835	23.6	13 123	15.0
40 to 49	26 046	26.9	17 496	20.0
≥50	40 697	42.0	46 346	52.9
Median, y	46		51	
Time period				
1965–1974	4467	4.6	949	1.1
1975–1984	13 139	13.6	5218	6.0
1985–1994	15 136	15.6	15 328	17.5
1995–2008	64 068	66.2	66 069	75.5
Socioeconomic status				
Farmer	1395	1.4	1286	1.5
Manual worker	39 620	40.9	30 548	34.9
Blue collar	27 276	28.2	22 660	25.9
Professional	6697	6.9	7536	8.6
Private	3419	3.5	3171	3.6
Others	18 403	19.0	22 363	25.5
Region				
Large city	31 388	32.4	33 267	38.0
Southern Sweden	44 517	46.0	37 503	42.8
Northern Sweden	20 286	21.0	15 851	18.1
Unknown	619	0.6	943	1.1
Without sibling	14 714	15.2	14 610	16.7
With sibling				
Sibling history	4993	5.2	4929	5.7
No history	77 103	79.6	68 025	77.6
All	96 810	100.0	87 564	100.0

VTE indicates venous thromboembolism; VVs, varicose veins.

Table 3. Basic Characteristics Among Spouses With VVs and VTE

Basic Characteristics	VVs		VTE	
	n	%	n	%
Sex				
Male	54 906	29.3	104 489	46.82
Female	132 480	70.7	118 670	53.18
Age, y				
<30	6222	3.32	6889	3.09
30 to 39	26 164	13.96	12 149	5.44
40 to 49	38 806	20.71	19 315	8.66
≥50	116 194	62.01	184 806	82.81
Median, y	54		68	
Period				
1965–1974	28 461	15.19	7317	3.28
1975–1984	42 783	22.83	33 630	15.07
1985–1994	32 568	17.38	60 414	27.07
1995–2008	83 574	44.6	121 798	54.58
Socioeconomic status				
Farmer	1298	0.69	2264	1.01
Manual worker	48 597	25.93	62 348	27.94
Blue collar	41 410	22.1	57 270	25.66
Professional	13 828	7.38	21 114	9.46
Private	4353	2.32	6686	3
Others	77 900	41.57	73 477	32.93
Region				
Large city	63 795	34.04	82 437	36.94
Southern Sweden	71 554	38.19	86 925	38.95
Northern Sweden	31 964	17.06	35 481	15.9
Unknown	20 073	10.71	18 316	8.21
Sibling history				
Yes	7596	4.1	7578	3.4
No	179 790	95.9	215 581	96.6
All	187 386	100.0	223 159	100.0

VTE indicates venous thromboembolism; VVs, varicose veins.

Table 4. Risk of VTE in Subjects With Siblings Diagnosed With VVs

	VT			PE			OVTE			All VTE		
Disease in Siblings	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Uncomplicated VVs	2443	1.35*	1.29 to 1.40	917	1.16*	1.08 to 1.23	879	1.18*	1.11 to 1.26	4240	1.27*	1.23 to 1.30
Complicated VVs	456	1.70*	1.55 to 1.87	166	1.40*	1.19 to 1.63	174	1.57*	1.35 to 1.82	796	1.60*	1.49 to 1.72
All VVs	2841	1.38*	1.33 to 1.43	1062	1.18*	1.11 to 1.25	1025	1.21*	1.14 to 1.29	4929	1.30*	1.26 to 1.33

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 5. Risk of VVs in Subjects With Siblings Diagnosed With VTE

	Complicated VVs			Uncomplicated VVs			All VVs		
Disease in Siblings	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
VT	438	1.61*	1.46 to 1.77	2548	1.38*	1.33 to 1.43	2995	1.41*	1.36 to 1.46
PE	162	1.30*	1.11 to 1.52	975	1.18*	1.10 to 1.25	1141	1.19*	1.12 to 1.26
OVTE	167	1.45*	1.24 to 1.69	931	1.21*	1.13 to 1.29	1100	1.24*	1.16 to 1.31
All VTE	720	1.46*	1.35 to 1.57	4258	1.28*	1.24 to 1.32	4993	1.30*	1.27 to 1.34

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

1985–1994, and 1995–2008). Socioeconomic status was assessed in terms of occupation, divided into 6 groups according to the Swedish socioeconomic classification of Statistics Sweden: farmer, blue-collar worker, manual worker, professional, private, and others (economically inactive individuals, including unemployed individuals and homemakers). Geographic region of residence was included to adjust for possible regional differences in admissions. It was categorized as "large city," "southern Sweden," and "northern Sweden." Large cities were defined as cities with a population of >200 000 and comprised the 3 largest cities in Sweden: Stockholm, Gothenburg, and Malmö.

Statistical Analysis

Familial risks were analyzed, as described previously.[14–18,25,42] Person-years at risk (ie, number of persons at risk multiplied by

Table 6. Risk of VTE and VVs by Age at Diagnosis and Number of Affected Siblings

Disease in Siblings	O	SIR	95% CI	O	SIR	95% CI
Risk of varicose veins						
Age at diagnosis, y	<40	≥40				
VTE	2568	1.34*	1.29 to 1.40	2425	1.26*	1.21 to 1.31
No. of affected siblings	1	≥2				
VTE	4619	1.28*	1.24 to 1.32	374	1.70*	1.53 to 1.88
Risk of venous thromboembolism						
Age at diagnosis, y	<40	≥40				
VVs	1731	1.32*	1.26 to 1.38	3198	1.28*	1.24 to 1.33
No. of affected siblings	1	≥2				
VVs	4495	1.28*	1.24 to 1.32	434	1.52*	1.38 to 1.67

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 7. Mortality Among Patients With VTE by Sibling History

	Cause-Specific Mortality			Overall Mortality		
Siblings' Diseases	Death	HR	95% CI	Death	HR	95% CI
VTE	106	1.60*	1.31 to 1.95	11 330	1.09*	1.07 to 1.11
VVs	69	0.88	0.69 to 1.13	11 829	0.99	0.97 to 1.01

HRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. HR indicates hazard ratio; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 8. Risk of VVs in Subjects With Spouses Diagnosed With VTE

	Complicated VVs			Uncomplicated VVs			All VVs		
Disease in Spouse	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Disease in husband									
VT	308	1.02	0.91 to 1.14	1794	1.06*	1.02 to 1.11	2124	1.06*	1.01 to 1.10
PE	263	1.06	0.93 to 1.19	1282	1.03	0.97 to 1.09	1565	1.03	0.98 to 1.08
OVTE	236	0.99	0.86 to 1.12	1267	1.06*	1.00 to 1.12	1529	1.05	1.00 to 1.11
All VTE	807	1.02	0.95 to 1.09	4343	1.05*	1.02 to 1.08	5218	1.05*	1.02 to 1.08
Disease in wife									
VT	225	1.19*	1.04 to 1.36	913	1.08*	1.02 to 1.16	1148	1.10*	1.04 to 1.17
PE	136	1.11	0.93 to 1.31	518	0.94	0.86 to 1.02	663	0.97	0.90 to 1.05
OVTE	96	1.01	0.82 to 1.24	463	1.09	0.99 to 1.19	568	1.08	0.99 to 1.17
All VTE	457	1.13*	1.02 to 1.23	1893	1.04	0.99 to 1.09	2378	1.06*	1.02 to 1.10

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

the time at risk) were calculated from the start of follow-up (January 1, 1964) until hospitalization for VTE or VVs, death, emigration, or the end of the follow-up (December 31, 2008).[43] Age-adjusted incidence rates were calculated for the whole follow-up period, divided into 5-year periods.[14–18,25] Standardized incidence ratios (SIRs) were used to measure the relative risk of VTE in persons with a sibling history of VVs (hospitalization or death) compared with those without a sibling history

Table 9. Risk of VTE in Subjects With Spouses Diagnosed With VVs

	VT			PE			OVTE			All VTE		
Disease in Spouse	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Disease in husband												
Uncomplicated VVs	907	1.03	0.96 to 1.09	525	0.90	0.82 to 0.98	463	1.05	0.95 to 1.15	1894	0.99	0.95 to 1.04
Complicated VVs	227	1.15*	1.01 to 1.31	135	1.03	0.86 to 1.22	97	0.97	0.79 to 1.19	459	1.07	0.98 to 1.18
All VVs	1144	1.05	0.99 to 1.11	669	0.93	0.86 to 1.00	569	1.04	0.95 to 1.13	2381	1.01	0.97 to 1.05
Disease in wife												
Uncomplicated VVs	1786	1.06*	1.01 to 1.11	1277	1.03	0.97 to 1.09	1258	1.07*	1.01 to 1.13	4321	1.05*	1.02 to 1.08
Complicated VVs	309	1.08	0.96 to 1.20	263	1.08	0.95 to 1.22	236	0.97	0.85 to 1.11	808	1.04	0.97 to 1.12
All VVs	2117	1.06*	1.01 to 1.11	1560	1.04	0.99 to 1.09	1520	1.06*	1.00 to 1.11	5197	1.05*	1.02 to 1.08

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 10. Risk of Venous Thromboembolism When Siblings Were Diagnosed With VVs by Sex

	Male			Female		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI
Uncomplicated VVs	2079	1.25*	1.2 to 1.31	2161	1.28*	1.22 to 1.33
Complicated VVs	399	1.61*	1.45 to 1.77	397	1.6*	1.44 to 1.76
All VVs	2417	1.28*	1.23 to 1.33	2512	1.31*	1.26 to 1.36

SIRs are adjusted for age, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VVs, varicose veins.
*95% CI does not include 1.00.

Table 11. Risk of Varicose Veins When Siblings Were Diagnosed With VTE by Sex

	Male			Female		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI
VT	956	1.5*	1.4 to 1.59	2039	1.37*	1.31 to 1.43
PE	377	1.29*	1.16 to 1.43	764	1.15*	1.07 to 1.24
OVTE	376	1.4*	1.26 to 1.54	724	1.17*	1.08 to 1.25
All VTE	1614	1.39*	1.33 to 1.46	3379	1.26*	1.22 to 1.31

SIRs are adjusted for age, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism.
*95% CI does not include 1.00.

of VTE. Similar calculations were performed separately for spouses.

Familial SIRs were calculated as the ratio of observed (O) and expected (E) numbers of VTE or VV cases using the indirect standardization method:[43]

$$\mathrm{SIR} = \frac{\sum_{j=1}^{J} O_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*}$$

In this method, $O{=}\sum O_j$ denotes the total number of observed cases in the study group; E^* (expected number of cases) is calculated by applying stratum-specific standardized incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; O_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by cross-classification of the following adjustment variables: age (5-year groups), sex, socioeconomic status, time period, and geographic region of residence.[43] The 95% CIs were calculated assuming a Poisson distribution.[43]

Cause-specific and overall mortality hazard ratios (HRs) were calculated using Cox regression.

Data are accurate to 2 decimals places. All analyses were performed using SAS version 9.2 (SAS Institute).

Table 12. Risk of VVs When Siblings Were Diagnosed With VTE Excluding Pregnancy-Related VVs

	VVs		
Siblings' Diseases	O	SIR	95% CI
VT	1734	1.53*	1.46 to 1.60
PE	682	1.30*	1.20 to 1.40
OVTE	634	1.31*	1.21 to 1.41
All VTE	2885	1.40*	1.35 to 1.45

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 13. Risk of VTE When the Siblings Were Diagnosed With VVs Excluding Pregnancy-Related VVs

	All VTE		
Siblings' Diseases	O	SIR	95% CI
Uncomplicated VVs	2095	1.32*	1.26 to 1.38
Complicated VVs	903	1.61*	1.51 to 1.72
All VVs	2929	1.38*	1.33 to 1.43

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 14. Risk of Venous Thromboembolism When Siblings Were Diagnosed With VVs by Country of Birth

	Sweden			European			Others		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Uncomplicated VVs	4157	1.26*	1.23 to 1.30	70	1.27	0.99 to 1.61	13	2.25*	1.19 to 3.86
Complicated VVs	786	1.61*	1.50 to 1.73	9	1.15	0.52 to 2.19	1	1.42	0.00 to 8.14
All VVs	4837	1.30*	1.26 to 1.33	78	1.25	0.99 to 1.57	14	2.18*	1.19 to 3.67

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VVs, varicose veins.
*95% CI does not include 1.00.

Table 15. Risk of Varicose Veins When Siblings Were Diagnosed With VTE by Country of Birth

	Sweden			European			Others		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
VTE	2944	1.42*	1.37 to 1.47	45	1.15	0.84 to 1.54	6	1.12	0.40 to 2.46
PE	1119	1.19*	1.12 to 1.27	19	1.12	0.68 to 1.76	3	1.52	0.29 to 4.51
OVTE	1080	1.24*	1.17 to 1.31	18	1.11	0.66 to 1.76	2	0.97	0.09 to 3.58
All VTE	4905	1.31*	1.27 to 1.34	77	1.10	0.87 to 1.38	11	1.20	0.60 to 2.16

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VTE, venous thromboembolism.
*95% CI does not include 1.00.

Results

Baseline characteristics for individuals included in the sibling analysis are presented in Table 2. A total of 87 564 patients were diagnosed with VTE (Table 2). The median age was 51 years. A total of 96 810 patients were diagnosed with VVs (Table 2). The median age was 46 years. In Table 3, baseline characteristics are presented for those included in the spouse analysis.

Shared Familial Susceptibility Among Siblings

Subjects with a sibling with VVs had an increased risk for VTE (Table 4). The overall SIR was 1.30. The familial risk was increased for venous thrombosis of the legs (SIR 1.38), pulmonary embolism (SIR 1.18), and other forms of venous thromboembolism (SIR 1.21). Sibling history of both complicated and uncomplicated VTE was associated with an increased risk for VTE. Sibling history of complicated VVs was associated with a higher risk of VTE than sibling history of uncomplicated VVs (SIR 1.60 versus SIR 1.27).

The reverse association was also significant (Table 5). Subjects with a sibling with VTE had an increased risk for VVs. The overall SIR was 1.30, and the risk was increased for both complicated VVs (SIR 1.46) and uncomplicated VVs (SIR 1.28). Sibling histories of VT, pulmonary embolism, and other forms of venous thromboembolism were all associated with an increased risk for VVs.

Table 16. Risk of VVs When Siblings Were Diagnosed With VTE Using Main and Secondary Diagnosis

	VVs		
Siblings' Diseases	O	SIR	95% CI
VT	3550	1.4*	1.36 to 1.45
PE	1356	1.14*	1.08 to 1.2
OVTE	1349	1.22*	1.16 to 1.29
All VTE	5950	1.28*	1.25 to 1.31

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 17. Risk of VTE When Siblings Were Diagnosed With VVs Using Main and Secondary Diagnosis

	All VTE		
Siblings' Diseases	O	SIR	95% CI
Uncomplicated VVs	5035	1.25*	1.21 to 1.28
Complicated VVs	981	1.54*	1.44 to 1.63
All VVs	5887	1.27*	1.24 to 1.31

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Table 18. Risk of Venous Thromboembolism When Siblings Were Diagnosed With VVs by Year of Diagnosis

	<2000			2001 or Later		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI
Uncomplicated VVs	1790	1.24*	1.18 to 1.30	2450	1.30*	1.25 to 1.35
Complicated VVs	356	1.64*	1.48 to 1.82	440	1.59*	1.45 to 1.75
All VVs	2089	1.27*	1.22 to 1.33	2840	1.33*	1.28 to 1.38

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VVs, varicose veins.
*95% CI does not include 1.00.

Familial Risks According to Age and Number of Affected Siblings

The highest risk for VTE (SIR 1.52) was observed in subjects with 2 or more siblings with VVs (Table 6). The SIR for VTE in those aged younger than 40 years was 1.32, and the SIR for VVs in those aged 40 years or older was 1.28.

The highest risk for VVs (SIR 1.70) was observed in subjects with 2 or more siblings with VTE (Table 6). The SIR for VVs in those aged younger than 40 years was 1.34, and the SIR for VVs in those aged 40 years or older was 1.26.

Mortality in Patients With a Sibling History of VTE or VVs

A multivariate survival analysis using Cox regression with HRs for overall death and VTE-related death was performed (Table 7). A sibling history of VTE increased VTE cause-specific mortality (HR 1.60, 95% CI 1.31 to 1.95) and, slightly, overall mortality (HR 1.09, 95% CI 1.07 to 1.11). Family history of VVs did not affect VTE cause-specific mortality (HR 0.88, 95% CI 0.69 to 1.13) or overall mortality (HR 0.99, 95% CI 0.97 to 1.01).

Familial Risks Among Spouses

To investigate the contribution of shared adult family environment, spouse effects were assessed. Among spouses, only slightly increased risks were observed (Tables 8 and 9). In spouses of VTE patients, a minor increase in risk of VVs was observed (SIR 1.05 for husbands, SIR 1.06 for wives). The risk of VTE in spouses of VV patients was similarly small (SIR 1.01 for husbands, SIR 1.05 for wives).

Additional Analysis

Stratified analysis was performed according to sex. The sex-specific familial risks were increased for both males and females (Tables 10 and 11). We also excluded VVs cases related to pregnancy (Tables 12 and 13). The familial risks were similar, although a tendency for slightly higher familial risks was observed. The risk for VTE was 1.38 (95% CI 1.33 to 43) after exclusion of pregnancy-related varicose veins.

Stratified analysis was also done according to country of birth, which did not change the results compared with Swedish-born individuals (Tables 14 and 15). A similar tendency for increased familial risks was noted for immigrants born in Europe as well as for those born in countries outside Europe; however, there were few familial cases, and most familial risks were not significant (Tables 14 and 15).

Sensitivity Analysis

We included only main diagnoses because the validity is generally higher for main diagnoses in the Swedish Hospital

Table 19. Risk of Varicose Veins When Siblings Were Diagnosed With VTE by Year of Diagnosis

	<2000			2001 or Later		
Siblings' Diseases	O	SIR	95% CI	O	SIR	95% CI
VT	1373	1.51*	1.43 to 1.59	1622	1.38*	1.31 to 1.44
PE	549	1.30*	1.19 to 1.41	592	1.15*	1.06 to 1.25
OVTE	509	1.31*	1.19 to 1.42	591	1.22*	1.13 to 1.33
All VTE	2300	1.39*	1.33 to 1.44	2693	1.28*	1.23 to 1.33

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism.
*95% CI does not include 1.00.

Table 20. Risk of VVs When the Siblings Were Diagnosed With VTE Excluding Those Without Siblings

	VVs		
Siblings' Diseases	O	SIR	95% CI
VT	2995	1.40*	1.35 to 1.45
PE	1141	1.18*	1.12 to 1.25
OVTE	1100	1.23*	1.15 to 1.30
All VTE	4993	1.29*	1.26 to 1.33

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; OVTE, other forms of venous thromboembolism; PE, pulmonary embolism; SIR, standardized incidence ratio; VT, venous thrombosis of the legs; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Discharge Register. A sensitivity analysis with inclusion of both main and secondary diagnoses gave similar results (Tables 16 and 17).

The outpatient register is available only from 2001. A sensitivity analysis showed that the familial risks were increased in the periods 1964–2000 and 2001–2008 (Tables 18 and 19). The results were not different to any major degree.

In the sibling analysis, all persons were included, even those without a sibling. Consequently, we performed a sensitivity analysis with exclusion of those who had no sibling. The familial risks, however, were very similar (Tables 20 and 21).

Discussion

To our knowledge, this is the first nationwide study to assess the familial risk of VTE in relation to VVs. The associations we found between VVs and VTE show that VVs and VTE share familial susceptibility. The low spousal risks suggest only a minor contribution of nongenetic shared environmental factors in adults.[36] The higher familial risk for those with 2 affected siblings also suggests that genetic factors might be involved in the sharing of familial susceptibility by VTE and VVs. Consequently, the observed increase in the risk of VTE in patients with VVs might have not only a familial background but possibly also a genetic background.[7,8]

Table 21. Risk of VTE When Siblings Were Diagnosed With VVs Excluding Those Without Siblings

	All VTE		
Siblings' Diseases	O	SIR	95% CI
Uncomplicated VVs	4240	1.27*	1.23 to 1.31
Complicated VVs	796	1.61*	1.50 to 1.73
All VVs	4929	1.30*	1.27 to 1.34

SIRs are adjusted for age, sex, time period, geographic region of residence, and socioeconomic status. O indicates observed number of cases; SIR, standardized incidence ratio; VTE, venous thromboembolism; VVs, varicose veins.
*95% CI does not include 1.00.

Mutations associated with thrombophilia have been linked to VVs accompanied by chronic leg ulcers[27–30]; however, only one small study of 27 patients with VVs has investigated the possible association between thrombophilic mutations and VVs without chronic leg ulcers.[30] Another study found an association between a mutation in thrombomodulin and VVs, but no association of the same mutation with VTE was found.[26] The results of the present study are in harmony with those studies that found an association between familial thrombophilia and chronic leg ulcers[27–30] and suggests the need for larger studies of the importance of thrombophilic mutations in patients with chronic leg ulcers. It is also possible that unknown vessel wall-related genetic risk factors for VVs might be risk factors for VTE. It is worth highlighting the association between VVs and not only VT but also pulmonary embolism and thrombosis at sites other than the legs and lungs (Tables 4 and 5).

Family history of VTE in the Swedish population is a relatively specific risk factor for venous disorders (ie, VTE and VVs).[14–19,25,36,44] We found weak or no associations, for example, between family history of VTE and risk for coronary heart disease or myocardial infarction, ischemic stroke, cancer, and pre-eclampsia or eclampsia in the Swedish population.[45–48] In contrast, venous thrombosis of the legs and pulmonary embolism share familial susceptibility not only with each other but also with rare forms of VTE. In Sweden, the major familial causes of venous disease are clearly different from the major familial causes of coronary heart disease or myocardial infarction, ischemic stroke, cancer, and pre-eclampsia or eclampsia.

The present study has a number of strengths. These include nationwide coverage in a country with high medical standards and diagnosis of patients by specialists during extended examinations in clinics.[36] In addition, the results were not affected by recall bias because the analyses were based exclusively on diagnosed cases. Importantly, the Multigeneration Register is a validated data source that has been proven to be reliable in the study of many familial diseases.[14–19,25,36,37,49] Data in the data set are almost 100% complete. The study design has been successfully used in a number of studies to determine familial risks for complex diseases, including VTE and VVs.[14–19,25,36]

The present study also has a number of limitations. Although it covers the 45-year period between 1964 and 2008, the Swedish Hospital Discharge Register contains complete data for only the period since 1987; therefore, events that occurred before 1964 and some events that occurred between 1964 and 1986 are missing. This probably

created a nondifferential bias regarding familial risks estimates. Another potential limitation is our lack of information on the methods used to diagnose patients; however, the Swedish Hospital Discharge Register has high validity, especially for cardiovascular disorders such as VTE, stroke, and myocardial infarction (≈95%).[36–41] Moreover, only cases in which the main diagnosis was VVs or VTE were analyzed to ensure that the analyses were of high quality. A further limitation is that outpatient data were available only for 2001–2008, which may have caused a nondifferential bias; however, subanalyses for the periods 1964–2000 and 2001–2008 showed similar risks (Tables 18 and 19). Moreover, incidence rates were calculated for the whole follow-up period, divided into 5-year periods, and adjustments were made for possible changes in incidence rate over time. Another possible limitation is that we had no data for risk factors for VTE or VVs. As a compromise, we adjusted the models for socioeconomic status (occupation). Moreover, family history is a risk factor for VTE, even in the presence of provoking risk factors like surgery, injury, pregnancy, and oral contraceptive use.[12]

An important limitation is that VVs and VTE may occur in the absence of symptoms. In the present study, we focused on the first symptomatic manifestation of VV or VTE. If many cases without these conditions actually have undiagnosed VVs or VTE, this could bias the familial risks. Some selective factors may have resulted in the increased rates of VVs or VTE to favor relatives; for instance, if a relative is treated successfully, this may encourage their spouse or sibling to seek similar medical advice. Affordability of health care and the likelihood of seeking medical advice are probably not limiting factors in Sweden because all residents have equal access to almost free health care. The low spousal risk suggests that selection bias for health care seeking in certain families is not a major problem.

Although the present study was limited to Sweden, stratified analysis of familial risks in siblings of persons born outside Sweden gave similar estimates, although the confidence interval was wide due to limited numbers of cases (Tables 14 and 15). This suggests that similar findings might be expected in other populations. The Swedish population is, for instance, genetically closely related to German and British people, and the results from Swedish nationwide family studies are likely to be valid for many persons of white origin in Europe and the United States.[36,50,51] Generalizability to other countries remains to be determined.

The results of the present study show that VTE and VVs share familial susceptibility. In some families, the familial aggregation of these disorders is relatively strong, and this, together with the low risks among spouses, suggests that VVs and VTE share familial susceptibility and possibly genetic factors.

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Disclosures

None.

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