



## Full Length Article

# A sibling based design to quantify genetic and shared environmental effects of venous thromboembolism in Sweden



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## ABSTRACT

**Introduction:** Few large studies have examined the heritability of venous thromboembolism (VTE). Moreover, twin studies have been suggested to overestimate heritability. The aim of the present study was to determine the heritability nationwide in the general Swedish population using full siblings and half-siblings.

**Methods:** VTE was defined using the Swedish patient register. Full sibling (FS) and half-sibling (HS) pairs born 1950–1990 were obtained from the Swedish Multi-generation Register. A maximum of 5 years age difference was allowed. We also required that the individuals within the pair should reside in the same household for at least 8 years or not at all (0 years) before the youngest turned 16. Information about sibling pair residence within the same household, small residential area, and municipality was obtained from Statistics Sweden. We assumed three potential sources of liability to VTE: additive genetic (A), shared (or common/familial) environment (C), and unique environment (E) components.

**Results:** Totally 881,206 FS pairs and 95,198 HS pairs were included. The full model predicted heritability for VTE with 47% for males and 40% for females. Environmental factors shared by siblings contributed to 0% of the variance in liability for both sexes, and unique environment (E) components accounted for 53% in males and 60% in females.

**Conclusion:** The high heritability of VTE risk indicates that genetic susceptibility plays a substantial role for VTE in the Swedish general population. Overestimation of heritability from twin studies is not likely. The proportion of the variance attributable to shared familial environment factors is small.

**Subject codes:** Genetics, epidemiology, thrombosis, cardiovascular disease, embolism

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## 1. Introduction

Venous thromboembolism [VTE] is a serious medical diagnosis which affects approximately 1–2 per 1000 individuals per year [1–3] and often runs in families. Familial thrombophilia, e.g. clustering of VTE, was recognized at the beginning of the 20th century [4]. Like many common human diseases and traits that cluster in families, VTE is considered to be a complex disorder influenced by several genetic and environmental factors [5,6]. Inherited deficiencies of the natural anticoagulant inhibitors antithrombin, protein C and proteins S, as well as activated protein C resistance (APC resistance) due to the FV Leiden mutation (rs6025) and the prothrombin 20210A mutation (rs1799963), have been associated with familial thrombophilia [5,6]. The five major identified genetic risk factors for VTE together account for only about 30% of the family history [7]. Newly identified common, but much

weaker, alleles probably only contribute to a fraction of the familial risk for VTE [8,9]. Thus, as for many other complex disorders, the source of the missing heritability of VTE remains to be determined.<sup>10</sup> The missing heritability of VTE might be genetic, epigenetic or non-genetic (due to familial environmental effects) [10]. Shared familial environmental factors might be related to socioeconomic factors such as poverty and low educational level but also health behaviours such as high alcohol consumption, drug abuse, smoking, physical inactivity, and unhealthy food habits [11].

Heritability of VTE, that is, the proportion of the variance attributable to genetic effects on VTE, has been estimated to be 50–60% in one twin study and two extended family studies [12–14]. However, the twin study was very small and non-significant for women [12]. There were only 11 concordant male monozygotic pairs and 8 dizygotic male pairs, one concordant female monozygotic pair and no dizygotic female pairs. However, the validity of the twin method has been questioned, with critics suggesting that the resulting heritability estimates might be inflated [15]. Twins also have a distinct shared intra-uterine experience and form, it is claimed, a unique psychological relationship so that results derived from them cannot be extrapolated to more typical human populations [15].

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The two previous extended family studies were mainly performed in selected families with idiopathic thrombosis or thrombophilia referred to specialist clinics [13,14]. Thus, limited data exist regarding the heritability of VTE in the general population.

The present study aims to determine the contribution of genetic factors (i.e. heritability), shared environment, and individual factors to the variance of VTE in a nationwide study of full siblings and half-siblings.

## 2. Material and methods

We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409). We used linked data from multiple Swedish nationwide registries and healthcare data [16–20]. Linking was achieved via the unique individual 10-digit personal ID number assigned at birth or immigration to all Swedish residents. In order to preserve confidentiality this ID number was replaced by a serial number. The following sources were used to create our database: the Total Population Register, containing annual data on family status; the Multi-generation Register, providing information on family relations; the Swedish Hospital Discharge Register, containing all hospitalizations for all Swedish inhabitants from 1987 to 2010 and partial data between 1964 and 1987; the Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2010; the Swedish Mortality Register, containing all causes of death; and the Population and Housing Censuses that provided information on household status in 1960, 1965, 1970, 1975, 1980, and 1985. In the database household was defined as follows: From 1960 to 1985 (every 5th year) we used the variable householdID from the Population and Housing Census. The householdID includes all individuals living in the same dwelling. For the years for which we did not have information, we approximated the householdID with the information from the year closest in time. From 1986 onwards (every year) we used the FamilyID from the Total Population Register. The FamilyID is defined by individuals that are related or married and who are registered at the same property (a person can only be part of one family). In addition, adults who are registered at the same property and have common children, but are not married, are registered in the same family.

The source population consisted of all individuals from the Swedish population who were born in Sweden between 1950 and 1990 and who had not emigrated or died prior to age 16. From the source population we selected all possible full- and half-sibling pairs with a maximum of 5 years age difference. We also required that the individuals within the pair should have resided in the same household for at least 8 years or 0 years before the youngest turned 16. Thus the included sibling pairs have shared household (more than 8 years) or have not shared household at all (0 years). For simplicity we stratified all the analyses based on gender, which means that all individuals within the pair had to have the same sex. The first census was 1960. We therefore assumed that siblings born 1950–1959 that cohabited in the 1960 census also had done so from birth. Siblings not living together in the 1960 census were assumed not to have shared the same household.

## 3. Ascertainment of VTE cases

Cases of VTE were classified according to the World Health Organization International Classification of Diseases (ICD-8, ICD-9, ICD-10). All types of VTE diagnosis were counted [12,19–22]. VTE was defined in the hospital discharge register and the mortality register, main and supplementary diagnoses, (between 1969 and 2010) by the following ICD codes: ICD-10: I63.6, I67.6, I80, I81, I82, I26, O222, O223, O225, O229, O870, O871, O873, O879, O882, O082, O087; ICD-9: 437G, 451, 452, 453, 415B, 416 W, 671C, 671D, 671E, 671F, 671X, 639G, 673C; ICD-8: 321, 450, 451, 452, 453, 671, 673.9; ICD-7: 463, 464, 465, 466, 583.00, 334.40, 334.50, 682, 684. It was also defined in the Outpatient Care Register (between 2001 and 2010) by the same ICD-10 codes as above. However, we required that the individual had at least 2 registrations

in the Outpatient Care Register in order to be defined as registered for VTE, due to lower validity of the outpatient register for VTE diagnosis, see below.

The Swedish Cause of Death Register contains data on cause and date of death from 1961 onwards and is fairly valid for a number of diagnoses [23,24]. In a validation study of the cause of death register among 1156 twins born in 1901–1925 the sensitivity was 89.5% and the confirmation rate was 70.8% for pulmonary embolism [23]. A high concordance of 89% was also found between hospital discharge diagnoses and the underlying causes of death in those who were hospitalized and later died [24]. The Swedish Hospital Discharge Register has nearly 90% overall validity or positive predictive values (PPV) [16–18,23]. The PPV for cardiovascular disorders such as VTE, myocardial infarction and stroke is around 90 to 95% [18–20]. In a Swedish study of males with VTE, hospital records were available for 304 cases (1970–1998) [25]. A total of 289 out of 304 (95%) cases with diagnosed VTE were judged to be diagnosed correctly [25]. Only 12 (3.9%) cases were not diagnosed with an objectively verified method but were treated with oral anticoagulation due to strong clinical probability. In total, 277 (91%) cases were objectively diagnosed with methods such as phlebography, ultrasound, CT scan and pulmonary scintigraphy [25]. The Outpatient Register has previously not been validated for VTE. Recently, Sultan et al. found that 43% of pregnant VTE cases first recorded as outpatient were not accompanied by anticoagulant prescriptions, whereas this proportion was much lower than those cases first recorded in the inpatient register (9%) [26]. Moreover, of cases of non-specific thrombophlebitis diagnoses, 25% had evidence of hirudoid (C05BA01) prescriptions. However, we have also used ATC codes for anticoagulant drugs (Supplement Table 1) to validate the outpatient and inpatient registers with prescription of anticoagulant drugs within 3 months after VTE diagnosis. The prescription register is only available from July 2005. PPV for inpatient diagnosis of VTE was 91%, which is similar to published data by Rosengren et al. and Sultan et al. [23,24]. A single outpatient diagnosis of VTE had less validity (60%), similar to Sultan et al. [24], but the presence of VTE diagnosis on two occasions in outpatients was associated with high PPV of 84% (i.e. anticoagulant prescription), similar to what was observed in the study by Rosengren et al. [25]. We therefore classified only outpatient diagnosis of VTE if diagnosis had occurred two times in outpatients, while one event of VTE in inpatient is enough to be classified as VTE. Supplement Table 2 shows the included VTE manifestations in the inpatient, outpatient, and death register.

## 4. Statistical methods

The familial relative risk (i.e., the ratio of the risks of those with and without a family history) was expressed as a recurrence risk ratio ( $\lambda$ ), which is the prevalence of the disease in relatives with affected relatives divided by the prevalence in the general population [19]. A measure of similarity in pairs of relatives of a particular type is the tetrachoric correlation. This is a measure in which one assumes an underlying binormal distribution of liability with multiple factors contributing additively and a threshold value that differs as a function of presence or absence of VTE. We assumed three potential sources of liability to VTE: additive genetic (A), shared (or common) environment (C), and unique environment (E) components, as previously described [15,27–29]. Shared environment reflects family and community experiences that increase similarity in siblings/half siblings raised together. Unique environment includes random developmental effects, environmental experiences not shared by siblings, and random error. The importance of A and C can be estimated from the patterns of sibling and half-sibling correlations. A is suspected when correlations in siblings are substantially greater than those seen in half siblings. C is likely to be present when the correlations in half siblings exceed half of those seen in full-sibling pairs (as this is the expected pattern if resemblance is due solely to genetic factors). In all our models we assumed different thresholds for males, females and sibling type. We also follow the recommendations

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