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Original Article

Cognitive ability in Swedish conscripts and future risk of venous thromboembolism: A co-relative prospective national study

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ABSTRACT

Objective: Cognitive ability measured via an IQ-test (intelligence quotient) has been associated with cardiovascular (CVD) incidence. Whether cognitive ability is associated with risk of venous thromboembolism (VTE) is unknown. The present nationwide co-relative study aims to determine whether cognitive ability in male conscripts is a predictor of VTE.

Methods: A Swedish cohort of male conscripts (n = 940,964) born in 1954–1970 with no history of previous VTE were followed from enlistment (1972–1990) until 2010. Data on cognitive ability, using an IQ-test at conscription, were linked with national hospital register data to calculate future risk of VTE requiring in-patient care. Using the Swedish Multi-Generation Register, we identified all full-siblings, half-siblings and first-cousin pair discordant for IQ. This co-relative design allows for adjustment for unmeasured shared genetic or environmental factors.

Results: A total of 5110 (0.54%) males were affected by VTE. IQ was associated with risk for VTE (hazard ratio = HR 0.87 95% confidence interval 0.84–0.89 per standard deviation [SD] increment). The association was highly time dependent with attenuation of effect over time and significant interaction between time and IQ. IQ was also associated with VTE in first-cousin pairs (HR = 0.74, 0.69–0.79) but not when examining discordant half-sibling pairs (HR = 0.94, 0.82–1.08), and only weakly in full-sibling pairs (HR = 0.91, 0.84–0.98).

Conclusions: The present study suggests that familial-shared environmental factors linked to cognitive ability might be involved in the etiology of VTE. However, it is unlikely that IQ by itself causes VTE.

1. Introduction

Venous thromboembolism (VTE) is the third most common cardiovascular disease [1,2]. In principle, all hypercoagulable states are due to disturbances in the blood flow (stasis), in the vessel wall or in the constituents of the blood, i.e. Virchows triad [1]. Multiple genetic and acquired risk factors for VTE have been described [1–3]. However, cognitive factors and VTE risk have not been studied although cognitive ability appears to be associated with arterial cardiovascular disorders (CVD), such as coronary heart disease and stroke and cognitive ability, which have been reported [4–7]. The cause of these associations is unclear but may be related to lifestyle and socioeconomic factors [8]. In a Swedish report it was suggested that it was unlikely that IQ (intelligence quotient) by itself causes the increased risk of arterial CVD [8]. Adjustment for especially poor childhood circumstances and behavioral factors measured in late adolescence, but also adult social circumstances, considerably weakened the association between IQ and arterial CVD. To the best of our knowledge, the influence of cognitive ability measured with an IQ test on the risk of VTE has not been determined. However, we have previously reported an association between such socioeconomic factors and VTE, i.e. low socioeconomic status, deprived neighborhood and alcoholism [9–11].

We hypothesized that cognitive ability might predict VTE in analogy with the situation for arterial CVD. The present study includes all Swedish males born during the period 1954–1970, who were enlisted for mandatory military service from the age of 18–20 years. The aim was to determine whether cognitive ability objectively measured with an IQ-test was associated with future risk of VTE requiring hospitalization. We adjusted for familial factors in a co-relative design, i.e. first-cousins, half-siblings, and full siblings in order to determine whether familial genetic or environmental factors are of importance for the possible association between IQ and VTE.

2. Methods

We used data from multiple Swedish nationwide registries linked by the unique individual Swedish 10-digit personal ID number assigned at birth or immigration to all residents in Sweden [12]. This ID number was

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replaced by a random number to preserve confidentiality. Our database was created from the following sources: the Total Population Register, containing annual data on family status [12–16]; the Multi-Generation Register, providing information on family relations; Swedish Hospital Discharge Register, containing all hospitalizations for Swedish inhabitants from 1964 to 2010; the Swedish Mortality Register, containing causes of death and the Military Conscription Register. The military service in Sweden was discontinued in 2010. The Swedish military service conscription examination involved a full medical assessment including cognitive function (IQ) measured by four subtests representing logical, spatial, verbal and technical abilities [8,17]. During the years covered by our study this examination was required by law; only men of foreign citizenship or those with a severe medical condition or disability were excluded. The global IQ score, derived from a summation of the four subtests, was standardized to give a Gaussian distributed score between one and nine. We translated this score into units with a mean of 0 and standard deviation of 1.

Individuals diagnosed with VTE according to the eighth (1969–1986), ninth (1987–1996) and tenth (1997–2010) versions of the International Classification of Diseases (ICD) were identified using hospital discharge data and mortality data. We used only the main diagnoses to guarantee high validity, which in the Hospital Discharge Register is around 95% for VTE and several other cardiovascular diseases [13,15,17]. VTE was defined by the following codes: pulmonary embolism (PE) ICD-8, 450; ICD-9, 415B and 416W; and ICD-10, I26); deep venous thrombosis (DVT) of the lower extremities ICD-8, 451; ICD-9, 451 (excluding 451A, i.e. superficial thrombophlebitis); and ICD-10, I80 (excluding I800, i.e. superficial thrombophlebitis). In a stratified analysis VTE were divided into cases with provoked and unprovoked VTE. Provoked VTE were proceeded by cancer, fracture or trauma, or surgery: diagnosis of any form of cancer in the Swedish Hospital Discharge Register within five years before or one year after their VTE diagnosis (cancer defined by ICD 10 codes: C00–C99; ICD 9 codes 140–208; ICD 8 codes 140–209); fractures or trauma three months prior (ICD 10: S00–S99, T00–T14 ICD 9: 800–929; ICD 8: 800–929); any surgery three months prior to VTE registration (hospitalization with any surgery code AAA–ZZZ or 0000–8999). The study was approved by the Ethics Committee of Lund University, Sweden (approval number 409/2008, with amendments approved on September 1, 2009 and January 22, 2010). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained but the presented data were anonymized thus eliminating any risk of identification.

The database began with all male individuals in the Swedish population born from 1951 to 1970, who were registered in the Military Conscription Register and had information on cognitive function. A total of 27 individuals had a VTE registration prior to their conscription examination. In total we analyzed 940,964 males; that is 95% of all male individuals born in Sweden during 1951–1970 who survived and resided in Sweden at age 19.

2.1. Statistical analysis

We used Cox proportional hazards models to investigate the future risk for VTE in individuals as a function of their cognitive ability. Robust standard errors were used to adjust the 95% confidence intervals (CIs) as we had several individuals from the same family. Follow-up time in number of years was measured from year of conscription examination until year of first registration for VTE, death, emigration or end of follow-up (year 2010), whichever came first. We investigated the proportionality assumption in all models; if this was not fulfilled we included an interaction term between IQ and time in the model. In a second step, we wanted to compare the results from the entire population with the results from a co-relative design. Using the Swedish Multi-Generation Register we identified all full-sibling pairs, all half-sibling pairs and all first cousin pairs with a maximum of five years age difference. Using stratified Cox proportional hazards models, we performed an analysis on all full-sibling pairs (N = 159,121 whereas 1638 were discordant for VTE), all half-sibling pairs (N = 33,011 whereas 404 were discordant for VTE), and all first cousin pairs (N = 196,000 whereas 1438 were discordant for VTE) that did not have the same IQ score from the conscription register, with a separate stratum for each relative pair. The co-relative design allows us to contrast the rates of VTE in relatives with different levels of IQ. The stratified Cox proportional hazards model provides a hazard ratio (HR) for VTE that is adjusted for the familial cluster and therefore accounts for an array of shared genetic and environmental factors. All statistical analyses were performed using SAS 9.3.

Table 1
Population and all VTE cases — Males born in Sweden 1951–1970 who were enlisted for military service between 1972 and 1990.

	N	All VTE	No VTE
Males	940,964	5110 (0.54%)[a]	
Mean age at first VTE (SD)		42.7 (8.9)	
Median follow-up (Q1; Q3)[b]		24 (18–31)	30 (25–36)
Person years		124,156	27,738,981
Mean (SD) IQ		−0.15 (1.00)	0.00 (1.00)
Mean age at start of follow-up		18.5 (0.9)	18.4 (0.9)

[a] 56% (n = 2.866) VTE cases were pulmonary embolism and 44% (2244) were deep venous thrombosis.
[b] Q1; Q3 = interquartile range.

3. Results

From 1972 until 1990 a total of 940,964 male conscripts, without previous VTE, were enlisted and performed an IQ-test. The baseline characteristics are presented in Table 1. All males were born during the period 1951–1970 and were 18–20 years old at enlistment. The overall follow-up time was 27,863,137 person years. A total of 5110 (0.54%) individuals were affected by VTE with a mean age of 42.7 years at first VTE event. Among these, 56% (n = 2866) VTE cases were due to PE and 44% (2244) were DVT. The mean (standardized) IQ at baseline, for those affected by VTE during follow-up, was −0.15 and 0.00 for those not affected by VTE during follow-up. In Fig. 1, the proportion of patients affected by VTE during follow-up (y-axis) is plotted against the distribution of the IQ at baseline (x-axis). The proportion of patients affected with VTE increased among individuals with low IQ. In Fig. 2, the Kaplan–Meir curves for different levels of the IQ are presented. A graded dose response is observed with highest VTE risk for those with IQ below two standard deviations. An exception was males with an IQ above two standard deviations. Although their VTE risk was lowest during the first 30 years of follow-up; they had higher risk

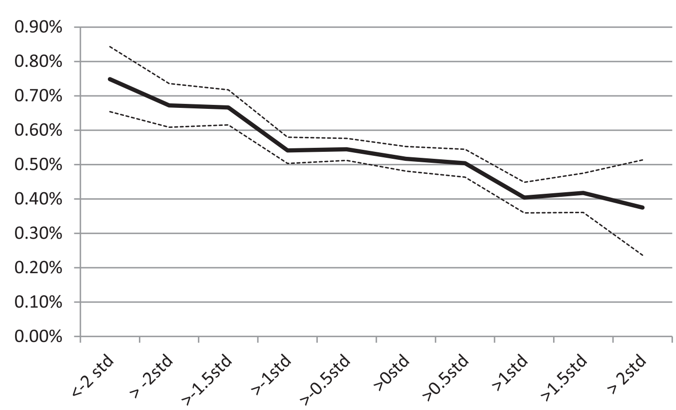

Fig. 1. Proportion of patients affected by VTE during follow-up (y-axis) and the distribution of IQ on x-axis.