Published in final edited form as:

Ann Med. 2017 March ; 49(2): 176–184. doi:10.1080/07853890.2016.1252057.

Cardiovascular fitness in young males and risk of unprovoked venous thromboembolism in adulthood

Bengt Zöller¹, Henrik Ohlsson¹, Jan Sundquist^{1,2}, and Kristina Sundquist¹

¹Center for Primary Health Care Research, Lund University, Malmö, Sweden

²Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, USA

Abstract

Background—Whether high cardiovascular fitness is associated with reduced risk of venous thromboembolism (VTE) is unknown. The present study aims to determine whether high cardiovascular fitness reduces the risk of VTE.

Methods—A Swedish cohort of male conscripts (n=773925) born in 1954–1970 with no history of previous VTE were followed from enlistment (1972–1990) until 2010. Data on cardiovascular fitness using a cycle ergonometric test (maximal aerobic workload in Watt [Wmax]) at conscription were linked with national hospital register data and the Multi-Generation Register. We identified all full-siblings and first-cousin pairs discordant for maximal aerobic workload. This co-relative design allows for adjustment for familial resemblance.

Results—In total, 3005 (0.39%) males were affected by VTE. Cardiovascular fitness estimated with Wmax was not associated with VTE risk when adjusted for body mass index (BMI). However, cardiovascular fitness estimated with Wmax/kg and adjusted for BMI was associated with reduced risk for VTE (Hazard ratio 0.81, 95% confidence interval 0.78–0.85 per standard deviation compared to mean Wmax/kg). The association was weaker over time and also when examining discordant first cousins and full-sibling pairs.

Conclusions—These results suggest that there is a relationship between cardiovascular fitness and weight that is important for future VTE risk.

Keywords

Epidemiology; Exercise; Genetics; venous thromboembolism

Correspondence to: Dr. Bengt Zöller, Center for Primary Health Care Research, CRC, Building 28, Floor 11, Entrance 72, Skåne University Hospital, SE-205 02 Malmö, Sweden, Cell phone: +46 70-6691476, Fax: +46 40-391370, bengt.zoller@med.lu.se.

DISCLOSURE OF INTEREST

The authors report no conflicts of interest.

ETHICAL APPROVAL

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.

INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disease (1,2). Prevention with anticoagulants is efficient but at the price of increased risk for major bleeding (2). Multiple genetic and acquired risk factors for VTE have been described (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). Conditions with venous stasis such as immobilization, bed rest in hospital and physical restriction increase the risk of VTE (1–4). Muscle activity of the legs have important physiological effects such as decreased venous pressure, increased venous flow and edema prevention (5–7). It is therefore reasonable to hypothesize that regular physical activity may prevent VTE. However, the association between physical activity and its opposite, physical inactivity, and VTE remain uncertain. A number of studies have been performed but the results are divergent (8–16). Results have shown lower as well as higher risk of VTE due to physical activity (Table 1). Several reasons may explain the divergent results in previous studies such as differences in study design, study populations, definitions of physical activity and limited statistical power. Estimating physical activity or inactivity with questionnaires or self-rating scales is another important limitation (17). Training and lack of regular physical activity significantly modifies the maximal oxygen uptake (i.e., maximal aerobic workload), though other factors like age, sex, weight, and genetics also are important (18). The maximal oxygen uptake might be measured directly (VO_{2max}) or in-directly (W_{max}) when running on a treadmill, exercising on a cycle, or using a so-called step test (18). However, no studies have determined the association between objectively measured cardiovascular fitness (maximal aerobic workload) and future VTE risk.

Moreover, no studies have determined whether cardiovascular fitness or physical activity at a young age is associated with future risk of VTE. There are generally low to moderate relationships between childhood and adolescent physical activity and adult physical activity (19). Nevertheless, the trends emphasize the importance of a lifestyle of regular physical activity during childhood and adolescence, which continues into and throughout adulthood (19). We hypothesized that objectively measured high cardiovascular fitness at a young age is associated with reduced future risk of unprovoked VTE. The present study includes all Swedish males born during the period 1954–1970 who were enlisted for mandatory military service at the age of 18–20 years. The aim was to determine whether cardiovascular fitness, objectively measured during ergometer cycling test, was associated with future risk of unprovoked VTE. For this purpose, we included a co-relative design in order to shed new light on potential causality.

MATERIAL AND METHODS

We used data from multiple Swedish nationwide registries linked by the unique individual Swedish 10-digit personal identity number assigned at birth or immigration to all residents of Sweden (20). This identity number was replaced by a random number to preserve confidentiality. Our database was created from the following sources (21–24): 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 Swedish inhabitants from 1964–2010; the Swedish Mortality Register, containing causes of death; the Military Conscription Register, containing among other things results from a cardiovascular fitness test and weight in kg (25). During the years covered by this study enlistment and examination was required by Swedish law. For men born in Sweden, only those with serious medical conditions or disabilities were excused. The cardiovascular fitness was assessed using a cycle ergonometric test. The procedure together with its reliability and validity has been previously described in detail (26). The procedure has been summarized by Åberg et al (25): “Briefly, after a normal resting electrocardiogram (ECG), 5 min of submaximal exercise was performed at work rates of 75–175W (Watt), depending on body mass. The work rate was continuously increased by 25W/min until volitional exhaustion. The individual was instructed to maintain pedal cadence between 60–70rpm (revolutions per minute, RPM). Heart rate was continuously measured. The final work rate or maximal aerobic workload (Wmax) is highly correlated with VO_{2max} (correlation of approximately 0.9) (27). In the material an increase in Wmax from 1985 and onwards was observed. Therefore we standardized Wmax into a Z-score with mean 0 and standard deviation 1 in order to account for differences over time.

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 (22,24,28). Moreover, we wanted to include primary thrombosis (main diagnosis) rather than secondary thrombosis, i.e., an additional diagnosis of VTE where other conditions were the main purpose for hospitalization. VTE was defined by the following codes: Pulmonary embolism (PE): ICD-8, 450; ICD-9, 415B and 416W; and ICD-10, I26; and 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). The following exclusion criteria were additionally applied: 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 to VTE (ICD10:S00–S99, T00–T14 ICD9: 800–929; ICD8: 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 included all male individuals in the Swedish population born during the period 1954 to 1970, who were registered in the Military Conscription Register, and had information for the cardiovascular fitness test as well as body weight. A total of 26 individuals had a VTE registration prior to their conscription examination and were excluded. In total we investigated 773,925 males; i.e. 84% of all male individuals born in

Sweden during 1954–1970 who survived and resided in Sweden at age 19. Note that for years 1978 and 1981 we did not have any information for Wmax (N=92,002).

Statistical analyses

Given that obesity is strongly associated with cardiovascular fitness as well as VTE we performed three different models in which we aimed to disentangle the effect of cardiovascular fitness from weight on future VTE risk. In the first approach we studied the association between Wmax and VTE, while controlling for Body Mass Index (BMI). In the second approach we studied the association between Wmax/Kg (standardized with mean 0 and StD 1) and VTE. For example, individuals with low Wmax and low body weight were treated similarly to individuals with high Wmax and high body weight in the analysis. Wmax/kg have in previous studies been shown to have high correlation with maximum oxygen consumption (VO2max) (correlation coefficient ≈ 0.9) (25,29,30). In the third approach we first performed a linear regression model where the outcome variable was Wmax and the predictor variable was body weight. The resulting residual (i.e., the difference between the observed Wmax and the predicted Wmax from the model) was used in the next step of the analysis and is called OE-score (observed – expected). For all three approaches we used Cox proportional hazards models to investigate the future risk for VTE in individuals as a function of their Wmax/Wmax/Kg or OE-score. Robust standard errors were used to adjust the 95% confidence intervals (CIs), as we had several individuals from the same families. 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. In all models we investigated the proportionality assumption; if this was not fulfilled we included an interaction term between the parameter of interest 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 (31). In order to examine whether any association between Wmax and VTE risk is due to causation a co-relative design can be used as an extension of a natural experiment. Traditionally, in this approach, the association between an exposure and an outcome is compared in the general population and in relatives. From the pattern of the associations in these two groups, it is possible to assess the degree to which the association observed in the population may be causal versus due to confounding from genetic and/or familial-environmental factors. If any association between high Wmax and VTE is truly causal, the expectation would be that the Wmax-VTE association would be of similar strength in the general population as in relative pairs discordant for their level of Wmax. We hypothesized that Wmax is a causal risk factor for VTE.

By means of the Swedish Multi-Generation Register; we identified all full-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 = 254,304) and all first-cousin pairs (N = 390,308) that did not have the same value of the predictor variable (i.e, Wmax/Wmax/Kg or OE-score) from the conscription register, with a separate stratum for each relative pair. The stratified Cox proportional hazards models 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.

RESULTS

From 1972 until 1990 we included a total of 773,925 male conscripts, without previous VTE, who were enlisted and performed a cycle ergonometric test. The baseline characteristics are presented in Table 2. All males were born during the period 1954–1970 and were aged 18–20 years old at enlistment. The total follow up time was 22,067,764 person years. A total of 3,005 (0.39%) individuals were affected by unprovoked VTE with a mean age of 41.1 years at first VTE event. In the present cohort 2,457 (82%) of VTE cases occurred before the age of 50 years (not shown in table). The overall incidence of VTE was 1.36 per 10,000 person years. Among these, 57% (n=1704) VTE cases were due to PE and 43% (1301) were due to DVT. The mean (unstandardized) Wmax at baseline, for those affected by VTE during follow-up, was lower than for those not affected by VTE during the follow up (260.0 vs. 266.4, $p<0.001$). The corresponding numbers for Wmax/Kg and OE-score also indicated a lower value for individuals with VTE during follow up. While Figure 1 illustrates that for Wmax/Kg and OE-score (OE = observed – expected) there seemed to be an increase in VTE among those with lower Z-scores (i.e., those individuals that were more than 1.5 standard deviations below the mean value), the prevalence of VTE was similar regardless of Wmax score.

The univariate Cox-models (Table 3) show that higher values of Wmax/Kg and the OE-score were associated with lower VTE risk (HR for Wmax/Kg was 0.76 (95% CI 0.73–0.79) and the HR for OE was 0.90 (95% CI 0.87–0.94)). However, the unadjusted HR for Wmax was low and also in the opposite direction with a slightly higher risk for individuals with high Wmax (HR 1.05, 95% CI 1.01–1.09). As expected, the adjustment for BMI decreased the strength of the association for all three predictor variables.

In all models the proportionality assumption was not entirely fulfilled. This suggests that the effect of the variable of interest changed over time. As seen in Table 3 the effect of Wmax/kg and OE-score decreased over time so that after 30 years of follow up the effect of the OE-score disappeared. For Wmax the association changed from negative in the beginning of the follow-up to a positive association at the end of the follow-up. Still, however, the effect was rather modest.

The results from the co-relative design showed that the effect of both Wmax/kg and OE-score decreased as we controlled for familial resemblance (i.e., among full-sibling pairs) (Table 4). For Wmax/Kg the HR was 0.86 (95% CI 0.79–0.94) among full siblings. The corresponding figure for the OE-score was 0.95 (95% CI 0.87–1.03). The models also show that the effect of Wmax/Kg and OE-score decreased over time in the full-sibling analysis, and for the OE-score the effect was non-significant at the end of the follow-up. Furthermore, the effect of Wmax was very close to 1 in the full sibling model, suggesting that there is no association between Wmax and VTE.

Subsidiary analysis

In order to analyse whether our results may be confounded by comorbidities, we excluded VTE patients with comorbidities included in a modified Charlson index (Supplementary Table 1). Totally, 937 VTE patients were excluded. A total of 2068 (0.27%) individuals were affected by VTE without having any of the comorbidities presented in Supplementary Table 1. The univariate Cox-models (Supplementary Table 2) show that a higher value of Wmax/Kg but not the OE-score were associated with lower VTE risk. The HR for Wmax/Kg was 0.83 (95% CI 0.79–0.87) and the HR for OE was 0.99 (95% CI 0.95–1.04). However, the unadjusted HR for Wmax went in the opposite direction with a slightly higher risk for individuals with high Wmax (HR 1.13, 95% CI 1.09–1.18). After adjustment for BMI, not only Wmax (1.10, 95% CI 1.06–1.15) but also the OE-score (1.05, 95% CI 1.01–1.10) was associated with increased VTE risk. Wmax/kg adjusted for BMI was still significantly associated with lower VTE risk (0.88, 95% CI 0.84–0.92).

The results from the co-relative design showed that the effect of Wmax/kg was unchanged as we controlled for familial resemblance (i.e., among full-sibling pairs) (Supplementary Table 3). For Wmax/Kg the HR was 0.83 (95% CI 0.79–0.87) among full siblings. The OE-score was not significant when controlling for familial resemblance (full-siblings pairs 0.95 (95% CI 0.86–1.05)). Furthermore, the effect of Wmax was not significant in the full sibling model (1.08, 95% CI 0.97–1.19), suggesting that there is no association between Wmax and VTE.

DISCUSSION

Consistent with previous studies on physical activity/inactivity (8–16) and VTE risk this study shows that the relationship between cardiovascular fitness and VTE is complex. While cardiovascular fitness measured by Wmax was not associated with VTE, higher values of Wmax/Kg were protective against VTE, even after 30 years of follow-up. Furthermore, when the association between Wmax/Kg and VTE was controlled for unmeasured familial factors, using a co-relative design, the weak association remained, suggesting a direct effect of low cardiovascular fitness on the risk for VTE. The association between Wmax/kg and VTE was still significant in all models even when VTE patient with comorbidities were excluded. Excluding VTE patients with comorbidities led to a stronger positive association between Wmax and VTE risk. However, this association was lost in the full sibling model when adjusting for familial resemblance suggesting no causality for this observation. These results suggest that there is a relationship between Wmax and body weight that is important for future VTE risk. In a further attempt to disentangle the effects of Wmax and body weight on VTE we found that individuals with a high OE-score (i.e., individuals that actually have a higher Wmax than would have been predicted by their body weight) also have a decreased risk for VTE, although not to a statistically significant extent when VTE patients with comorbidities were excluded. Altogether, these results show that Wmax on its own have no relationship with VTE albeit in relation to body weight. The results could be of importance due to the “The pandemic of physical inactivity” (32). If increased physical activity in adolescence could lead to high cardiovascular fitness in relation to body weight interventions aiming to increase physical activity in early life might contribute to a decrease in VTE

incidence, even in adulthood. However, the mechanisms of our observations are unknown. It might be related to that physical activity in young age correlates with physical activity in adulthood (19). However, we cannot exclude that our results is due to later-life obesity or other unfavorable lifestyles in individuals with low cardiovascular fitness at young age. Wattanakit et al found that after adjusting for BMI, physical activity was not associated with increased VTE risk (15). A vicious circle is often observed among overweight people. Overweight decreases maximal aerobic workload leading to less physical activity, which in turn further increases overweight (18).

The co-relative design suggests that the association between Wmax/Kg and VTE was partly a direct effect and partly confounded by familial factors. The same attenuation was seen for the OE-score. The OE-score effect was, however, lower in the population sample. Research has suggested that genetic factors are important determinants for physical activity, fitness and health (18,33). Genetic factors may contribute to up to 30% of the level of physical activity (33). The contribution of genetic factors to various components of health-related fitness varies between 20 and 50% (33). Moreover, Karvinen et al have suggested, based on both animal and human studies, that genetic pleiotropy partially explain the commonly reported associations between high baseline physical activity and subsequent decreased mortality (34). Despite suggestive results from observational studies, it has not been possible to demonstrate a beneficial effect of physical activity on mortality in carefully controlled intervention studies amongst subjects who have been healthy at baseline (34). Identification of the underlying genetic variance may be of importance for VTE risk (35). Presently, no genetic markers found in genome wide association studies (GWAS) for physical activity or inactivity have been found in GWAS for VTE (35,36). A Mendelian randomization study has shown that a SNP (FTO rs9939609 variant) for obesity is associated with increased VTE risk (37). It is possible that this variant also could affect Wmax/kg (37).

The present study has a number of strengths. These include nationwide coverage in a country of high medical standards surveilled by the Swedish National Board of Health and Welfare together with inpatient diagnoses of patients by specialist physicians during examinations in clinics. Data in the Swedish registers are remarkably complete. In 2001, personal identity numbers were missing in only 0.4% of hospitalizations and main diagnoses in 0.9% of hospitalisations (21). Importantly, the Multi-Generation Register is a validated source that has been proved to be reliable in the study of many familial diseases (23,24). In a Swedish study of males with VTE hospital records were available for 304 cases (28). A totally of 289 out of 304 (95%) cases with diagnosed VTE were judged to be diagnosed correctly (28). 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 (28).

This study does, however, have some limitations. We had no access to information about life-style factors such as smoking. Smoking is associated with the independent variable cardiovascular fitness, measured as maximum oxygen consumption (V02max) (38). The dependent variable VTE has in two recent systematic reviews been suggested to be associated with smoking (39,40). Thus, smoking is likely a potential confounder in the

present study. Nor had we information about waist and hip circumference or laboratory measurements such as lipids, hemoglobin, leucocytes, thrombocytes, creatinine, blood glucose and CRP. Another limitation is that lifestyle habits,¹⁹ medications and the presence of diseases may change during life. This may partly explain the decreased association between cardiovascular fitness and VTE risk that was observed over time. We included only main diagnosis in order to include primary thrombosis (main diagnosis) and not secondary thrombosis to other conditions. Thus, secondary DVT and PE due to co-morbidities were not included. This decreased the sensitivity for VTE but the hypothesis was not to study whether cardiovascular fitness reduces the risk of other diseases that indirectly could lead to decreased VTE incidence. One additional limitation is that we had no access to twin data in which we would have been able to control for 100% of the genetic resemblance and a major part of family environmental factors. We did not have access to data for thrombophilic defects, but the co-relative design adjusts for an array of shared genetic and environmental factors. A potential but most likely a non-differential bias is the introduction of low-molecular-weight heparin in 1994 and the treatment of many less severe DVT patients (especially distal thrombosis) as outpatients. Still, our study better reflects the more severe cases (proximal DVT) that still should be admitted to hospital. However, the introduction of outpatient treatment of DVT explains why PE was more common than DVT because all PE patients are still treated as inpatients in Sweden. A number of less severe DVT cases are treated as outpatient cases. If cases with low cardiovascular fitness tend to be more severe (i.e., hospitalized) than cases with high cardiovascular fitness, this could overestimate the VTE risk, but there is no evidence supporting this hypothesis. However, our data will reflect the risk for severe hospitalized cases.

A weakness of the study is that both W_{max}/kg and W_{max} are surrogate measures of the maximum oxygen consumption (V_{O2max}). However, both measures are determined with the used indirect method and strongly correlate ($r=0.9$) with directly measured maximum oxygen consumption (V_{O2max}) (25,27,29,30). Directly measured V_{O2max} , which is the golden standard, is more laborious but has been shown to be associated with progression of carotid atherosclerosis in middle-aged men and cognitive decline with aging (41,42). In addition, our analyses included W_{max}/Kg as well as only W_{max} as potential predictors for future VTE as well as a co-relative design, which increased our possibilities to shed new light on potential causality. We did not adjust for comorbidity; rather, we excluded cases secondary to major provoking factors, i.e., cancer, trauma, fracture, and surgery. Moreover, the inclusion of only main diagnoses of VTE events further helped to secure the inclusion of mainly unprovoked VTE. A limitation regarding generalizability is that the present study was limited to Sweden. However, the Swedish population is genetically closely related to, for instance, German and British populations, and the results from Swedish nationwide family studies are likely to be valid for many persons of Caucasian origin in Europe and the United States (23). However, the importance of cardiovascular fitness in females and in older males remains to be determined. The present study only included males and in the present cohort 2,457 (82%) of VTE cases occurred before age of 50 as the conscripts were born 1954–1970. However, in the general population it could be estimated that only 5–10% of all VTE cases occur before age of 50 years (1,24,43,44).

In conclusion, this is the first study to show an association between objectively tested cardiovascular fitness (Wmax/kg) at young age and risk of future unprovoked VTE. However, the association between cardiovascular fitness and future VTE risk is complex and potential mechanisms needs to be studied further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

FUNDING

This work was supported by grants awarded to Dr Bengt Zöller by the Swedish Heart-Lung Foundation, ALF funding from Region Skåne awarded to Dr Bengt Zöller and Dr Kristina Sundquist, grants awarded to Dr Bengt Zöller, Kristina Sundquist and Dr Jan Sundquist by the Swedish Research Council. The funders had no role in in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Research reported in this publication was also supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL116381 to Kristina Sundquist. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999; 353:1167–73. [PubMed: 10209995]
2. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet*. 2010; 376:2032–9. [PubMed: 21131039]
3. Laursen SB, Jensen TN, Bolwig T, Olsen NV. Deep venous thrombosis and pulmonary embolism following physical restraint. *Acta Psychiatr Scand*. 2005; 111:324–7. [PubMed: 15740470]
4. Schreijer AJ, Cannegieter SC, Doggen CJ, Rosendaal FR. The effect of flight-related behaviour on the risk of venous thrombosis after air travel. *Br J Haematol*. 2009; 144:425–9. [PubMed: 19036084]
5. Hjelmstedt A. The pressure in the veins of the dorsum of the foot in quiet standing and during exercise in limbs without signs of venous disorder. *Acta Chir Scand*. 1968; 134:235–44. [PubMed: 5730895]
6. Kugler C, Strunk M, Rudofsky G. Venous pressure dynamics of the healthy human leg Role of muscle activity, joint mobility and anthropometric factors. *J Vasc Res*. 2001; 38:20–9. [PubMed: 11173991]
7. Stick C, Jaeger H, Witzleb E. Measurements of volume changes and venous pressure in the human lower leg during walking and running. *J Appl Physiol*. 1992; 72:2063–8. [PubMed: 1629057]
8. van Stralen KJ, Le Cessie S, Rosendaal FR, Doggen CJ. Regular sports activities decrease the risk of venous thrombosis. *J Thromb Haemost*. 2007; 5:2186–92. [PubMed: 17697136]
9. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. *Contraception*. 2004; 70:3–10. [PubMed: 15208046]
10. Kabrhel C, Varraso R, Goldhaber SZ, Rimm E, Camargo CA Jr. Physical inactivity and idiopathic pulmonary embolism in women: prospective study. *BMJ*. 2011; 343:d3867. [PubMed: 21727169]

11. Lindqvist PG, Epstein E, Olsson H. The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study. *Br J Haematol*. 2009; 144:234–40. [PubMed: 19036105]
12. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*. 2005; 162:975–82. [PubMed: 16207808]
13. van Stralen KJ, Doggen CJ, Lumley T, Cushman M, Folsom AR, Psaty BM, et al. The relationship between exercise and risk of venous thrombosis in elderly people. *J Am Geriatr Soc*. 2008; 56:517–22. [PubMed: 18179500]
14. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002; 162:1182–9. [PubMed: 12020191]
15. Wattanakit K, Lutsey PL, Bell EJ, Gornik H, Cushman M, Heckbert SR, et al. Association between cardiovascular disease risk factors, occurrence of venous thromboembolism A time-dependent analysis. *Thromb Haemost*. 2012; 108:508–15. [PubMed: 22782466]
16. Borch KH, Hansen-Krone I, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, et al. Physical activity risk of venous thromboembolism The Tromso study. *Haematologica*. 2010; 95:2088–94. [PubMed: 20801904]
17. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L, et al. Assessment of physical activity-a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2010; 17:127–39. [PubMed: 20215971]
18. Åstrand, PO., Rodahl, K. Textbook of physiology: Physiological bases of exercise. 4. New York, NY: McGraw-Hill; 2003.
19. Malina RM. Physical activity and fitness: pathways from childhood to adulthood. *Am J Hum Biol*. 2001; 13:162–2. [PubMed: 11460860]
20. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009; 24:659–67. [PubMed: 19504049]
21. Rosen, M., Hakulinen, T. Use of disease registers. In: Ahrens, W., Pigeot, I., editors. *Handbook of epidemiology*. Springer-Verlag; Berlin: 2005. p. 231–252.
22. Ludvigsson JF, Andersson E, Ekblom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011; 11:450. [PubMed: 21658213]
23. Ekblom A. The Swedish Multi-generation Register. *Methods Mol Biol*. 2011; 675:215–20. [PubMed: 20949391]
24. Zöller B. Nationwide Family Studies of Cardiovascular Diseases - Clinical and Genetic Implications of Family History. *EMJ Cardiology*. 2013; 1:102–13.
25. Åberg MA, Waern M, Nyberg J, Pedersen NL, Bergh Y, Åberg ND, et al. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. *Br J Psychiatry*. 2012; 201:352–359. [PubMed: 22700083]
26. Nordesjö LO, Schele R. Validity of an ergometer cycle test and measures of isometric muscle strength when prediction some aspects of military performance. *Swed J Def Med*. 1974; 10:11–23.
27. Patton JF, Vogel JA, Mello RP. Evaluation of a maximal predictive cycle ergometer test of aerobic power. *Eur J Appl Physiol Occup Physiol*. 1982; 49:131–40. [PubMed: 7201925]
28. Rosengren A, Fredén M, Hansson P-O, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. *J Thromb Haemost*. 2008; 6:558–64. [PubMed: 18045241]
29. Glassford RG, Baycroft GH, Sedgwick AW, Macnab RB. Comparison of maximal oxygen uptake values determined by predicted and actual methods. *J Appl Physiol*. 1965; 20:509–13. [PubMed: 5319996]
30. Nordesjö LO. A comparison between the Thornvall maximal ergometer test, submaximal ergometer tests and maximal oxygen uptake. *Swed J Def Med*. 1974; 10:3–10.
31. Lawlor, DA., Mishra, GD. Family Matters: Designing, Analysing and Understanding Family-based Studies in Life Course Epidemiology. Oxford University Press; Oxford: 2009.

32. Kohl, HW3rd, Craig, CL., Lambert, EV., Inoue, S., Alkandari, JR., Leetongin, G., et al. The pandemic of physical inactivity: global action for public health. *Lancet*. 2012; 380:294–305. [PubMed: 22818941]
33. Lakka TA, Bouchard C. Genetics, physical activity, fitness and health: what does the future hold? *J R Soc Promot Health*. 2004; 124:14–5. [PubMed: 14971186]
34. Karvinen S, Waller K, Silvennoinen M, Koch LG, Britton SL, Kaprio J, Kainulainen H, Kujala UM. Physical activity in adulthood: genes and mortality. *Sci Rep*. 2015; 5:18259. [PubMed: 26666586]
35. de Vilhena e Santos DM, Katzmarzyk PT, Seabra AF, Maia JA. Genetics of physical activity and physical inactivity in humans. *Behav Genet*. 2012; 42:559–78. [PubMed: 22426782]
36. Morange PE, Suchon P, Trégouët DA. Genetics of Venous Thrombosis: update in 2015. *Thromb Haemost*. 2015; 114:910–9. [PubMed: 26354877]
37. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. *J Intern Med*. 2015; 277:573–84. [PubMed: 25161014]
38. McDonough P, Moffatt RJ. Smoking-induced elevations in blood carboxyhaemoglobin levels Effect on maximal oxygen uptake. *Sports Med*. 1999; 27:275–83. [PubMed: 10368876]
39. Zhang G, Xu X, Su W, Xu Q. Smoking and risk of venous thromboembolism: a systematic review. *Southeast Asian J Trop Med Public Health*. 2014; 45:736–45. [PubMed: 24974658]
40. Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG, Wu SH. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Med*. 2013; 10:e1001515. [PubMed: 24068896]
41. Lakka TA, Laukkanen JA, Rauramaa R, Salonen R, Lakka HM, Kaplan GA, Salonen JT. Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med*. 2001; 134:12–20. [PubMed: 11187415]
42. Wendell CR, Gunstad J, Waldstein SR, Wright JG, Ferrucci L, Zonderman AB. Cardiorespiratory fitness and accelerated cognitive decline with aging. *J Gerontol A Biol Sci Med Sci*. 2014; 69:455–62. [PubMed: 24192540]
43. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015; 12:464–74. [PubMed: 26076949]
44. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003; 107:I4–8. [PubMed: 12814979]

Key Messages

- Whether high cardiovascular fitness is associated with reduced risk of venous thromboembolism (VTE) is unknown.
- A Swedish cohort of male conscripts (n=773925) tested with a cycle ergometric test with no history of previous VTE were followed from enlistment (1972–1990) until 2010.
- Cardiovascular fitness estimated with Wmax/kg and adjusted for BMI was associated with reduced risk for VTE (HR 0.81, 95%CI 0.78–0.85).
- These results suggest that there is a relationship between cardiovascular fitness and weight that is important for future VTE risk.

Figure 1.
Proportion of patients affected by VTE during follow-up (y-axis) and Z-score on x-axis.

Summary of studies of physical activity and inactivity and risk of venous thromboembolism (VTE).

Table 1

Ist Author, Year, Country	Study design	VTE cases (N)	Age (mean or range)	Females (%)	Adjusted Risk (95% CI)	Main predictor
Tsai AW et al 2002 (14)	Cohort	215	59	55.1%	No association	Physical inactivity
Sidney S et al 2004 (9)	Case-control	196	15–44	100%	0.72; 0.52–1.00 0.50; 0.35–0.72	Regular physical activity Vigorous physical activity
Glynn RJ et al 2005 (12)	Cohort	352	40–84	0%	1.09 1.01, 1.18	Exercise frequency per one category
Van Stralen KJ et al 2007 (8)	Case-control	3608	47.6	54.4%	0.71; 0.64–0.78	Participating in sports activity
Van Stralen KJ et al 2008 (13)	Cohort	171	65	47.3%	1.16; 0.84–1.61 1.75 (1.08–2.83)	Mild exercise Strenuous exercise
Lindqvist PG et al 2009 (11)	Cohort	312	20–64	100%	0.4; 0.3–0.7	Strenuous exercise
Borch KH et al 2010 (16)	Cohort	460	25–97	52.4%	0.82; 0.60–1.11	Moderate amounts of exercise
Kabrhel C et al 2011 (10)	Cohort	268	30–55	100%	2.34; 1.30–4.20 P=0.53 for trend for activity	Physical inactivity Physical activity
Wattanakit K et al 2012 (15)	Cohort	468	54.1	55%	0.81 (0.62–1.06)	Physical activity

Bold text=a protective effect of physical activity. Italics = negative effect of physical activity.

Table 2

Population – Males born in Sweden 1954–1970 who were enlisted for military service between 1972 and 1990.

	N	VTE	No VTE
Males	773,925	3,005 (0.39%) ^a	770,920 (99.61%)
Age (years) at baseline (range)	18–20		
Mean age (years) at first VTE (SD)		41.1 (8.3)	
Median Follow-up (Q1; Q3) ^b		23 (17–30)	28 (24–34)
Person Years	22,067,764	68,676	21,999,088
Mean (SD) age at start of follow-up		18.3 (0.7)	18.2 (0.6)
Mean (SD) Wmax		260.0 (46.9)	266.4 (49.6)
Mean (SD) Wmax/Kg		3.616 (0.686)	3.877 (0.718)
Mean (SD) OE-score ^c		−12.5 (45.3)	0.005 (46.6)

^a57% (n=1704) VTE cases were pulmonary embolism and 43% (1301) were deep venous thrombosis.

^bQ1; Q3= interquartile range.

^cOE-score= the observed-expected-score is the residual from the difference between the observed Wmax and the predicted Wmax in a linear regression model.

Table 3

The observed hazard ratios (HRs) in the general population for VTE as the outcome with Wmax/WmaxKg/OE-score^b as exposure variables. The HRs represent one unit (one standard deviation) increase in the Z-score (N=773 925). The Z-score is the standardized Wmax/WmaxKg/OE-score with mean 0 and standard deviation 1.

	Wmax	Wmax/kg	OE-score ^b
Z-score (unadjusted)	1.05 (1.01; 1.09)	0.76 (0.73; 0.79)	0.90 (0.87; 0.94)
Z-score (adjusted for BMI)	1.02 (0.98; 1.06)	0.81 (0.78; 0.85)	0.99 (0.95; 1.02)
Interaction between Z-score and time			
Z-score	0.89 (0.80; 1.00)	0.66 (0.58; 0.74)	0.76 (0.69; 0.83)
Z-score*Time	1.01 (1.00; 1.01)	1.01 (1.00; 1.01)	1.01 (1.00; 1.01)
Z-score (Time 1) ^a	0.90 (0.81; 1.00)	0.66 (0.58; 0.74)	0.77 (0.69; 0.83)
Z-score (Time 10) ^a	0.96 (0.89; 1.03)	0.70 (0.65; 0.75)	0.82 (0.77; 0.87)
Z-score (Time 20) ^a	1.03 (0.99; 1.07)	0.75 (0.72; 0.78)	0.88 (0.85; 0.92)
Z-score (Time 30) ^a	1.10 (1.05; 1.15)	0.80 (0.76; 0.85)	0.96 (0.91; 1.00)

^aCalculated from the equation including Z-score and interaction between Z-score and time. Indicating the effect of Z-score at a particular time at follow-up.

^bOE-score= the observed-expected-score is the residual from the difference between the observed Wmax and the predicted Wmax in a linear regression model.

Table 4

The observed hazard ratios (HRs) in the cousin and full sibling sample for VTE as the outcome with Wmax/WmaxKg/OE-score^b as exposure variables. The HRs represent one unit (one standard deviation) increase in the Z-score (N=773 925). The Z-score is the standardized Wmax/WmaxKg/OE-score with mean 0 and standard deviation 1.

	Wmax	Wmax/kg	OE-score ^b
Unadjusted Z-score			
Population (Z-score)	1.05 (1.01; 1.09)	0.76 (0.73; 0.79)	0.90 (0.87; 0.94)
Cousins (Z-score; n=254,304)	1.05 (0.97; 1.15)	0.82 (0.77; 0.88)	0.93 (0.87; 0.99)
Full siblings (Z-score; n =390,308)	1.04 (0.98; 1.11)	0.86 (0.79; 0.94)	0.95 (0.87; 1.03)
Time dependence of Z -score			
Z-score (Time 1) – Cousins ^a	0.79 (0.66; 0.94)	0.68 (0.56; 0.81)	0.74 (0.61; 0.87)
Z-score (Time 10) – Cousins ^a	0.92 (0.83; 1.01)	0.74 (0.67; 0.83)	0.83 (0.75; 0.92)
Z-score (Time 20) – Cousins ^a	1.08 (1.01; 1.16)	0.83 (0.77; 0.89)	0.96 (0.90; 1.03)
Z-score (Time 30) – Cousins ^a	1.28 (1.11; 1.48)	0.92 (0.80; 1.05)	1.19 (0.99; 1.42)
Z-score (Time 1) – Siblings ^a	1.02 (0.81; 1.30)	0.84 (0.67; 1.06)	0.88 (0.70; 1.10)
Z-score (Time 10) – Siblings ^a	1.04 (0.90; 1.20)	0.85 (0.74; 0.98)	0.91 (0.80; 1.05)
Z-score (Time 20) – Siblings ^a	1.05 (0.96; 1.15)	0.86 (0.78; 0.94)	0.95 (0.87; 1.03)
Z-score (Time 30) – Siblings ^a	1.07 (0.93; 1.24)	0.87 (0.75; 1.01)	0.98 (0.85; 1.14)

^a Calculated from the equation including Z-score and interaction between Z-score and time. Indicating the effect of Z-score at a particular time at follow-up.

^b OE-score= the observed-expected-score is the residual from the difference between the observed Wmax and the predicted Wmax in a linear regression model.