Physical activity, immobilization and the risk of venous thrombosis

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Chapter 3

Regular sports activities decrease the risk of venous thrombosis

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Abstract

Background: Stasis of the blood has been postulated as a major cause of venous thrombosis. However, little is known about the effect of stimulating the blood flow in order to prevent venous thrombosis through for example sports activities.

Objectives: In a large population-based case-control study (MEGA-study) we studied whether participating in sports activities on a regular basis was associated with venous thrombosis risk.

Patients/Methods: Consecutive patients with a first venous thrombosis of the leg or a pulmonary embolism, and control subjects, consisting of partners of the patients and randomly selected control subjects from the general population, were asked to participate. Sports activities and other risk factors for venous thrombosis were reported in a standardized mailed questionnaire. Participants with malignancy were excluded.

Results: 1136 out of 3608 patients (31.5%) and 1686 out of 4252 control subjects (39.7%) participated in sports activities. Participating in sports activities reduced the risk of venous thrombosis compared with not participating in sports activities (odds ratio (OR) 0.64; 95% confidence interval (CI) 0.58-0.71). Risk reductions were similar after adjustment for sex, age and body mass index (OR_{adj} 0.71; 95% CI 0.64-0.78) and when the analysis was restricted to healthy individuals (OR_{adj} 0.67; 95% CI 0.58-0.78). No differences in risk were found for various frequencies, intensities and types of sport.

Conclusion: Regular sports activities reduce the risk of venous thrombosis.

Introduction

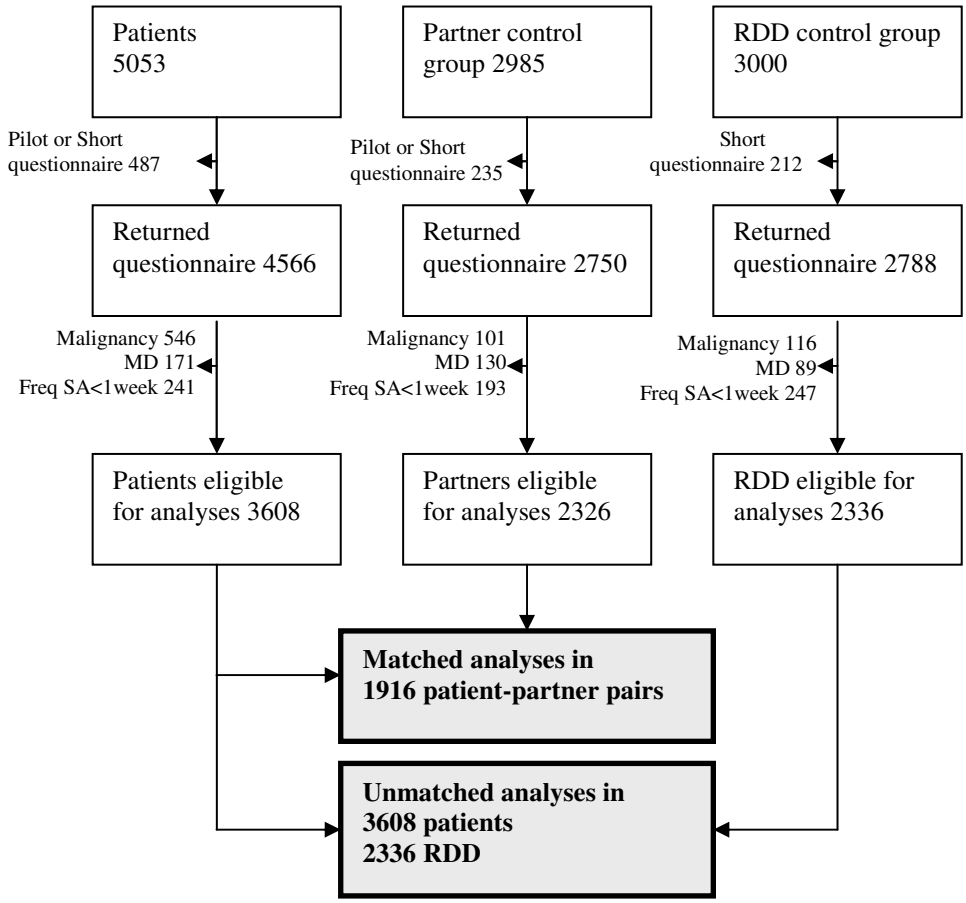
The incidence of a first venous thrombosis is about 1 to 3 per 1000 individuals per year [1,2]. The disorder commonly manifests as a deep vein thrombosis in the legs. Often embolisation occurs resulting in pulmonary embolism which can lead to death in about 1 to 2 percent. Venous thrombosis is a multicausal disease and several risk factors such as malignancy, oral contraceptive use and genetic mutations have been identified [3]. Apart from changes of the composition of the blood and damage of the vessel wall, stasis of the blood has been postulated by Virchow in 1856 as one of the three main causes of thrombosis [4]. Immobilization and physical restrictions are well-known causes of venous thrombosis [5-7]. However, little is known about the effect of stimulation of the blood flow,

i.e. physical activity [8]. In arterial disease, beneficial effects of physical activity have been observed for stroke, cardiac failure and myocardial infarction [9,10]. Furthermore, several studies have shown more beneficial coagulant state in individuals who exercise on a regular basis suggesting a possible beneficial effect on venous thrombosis risk [8,11-15].
We previously showed a beneficial effect of sports activities involving the legs on the risk of venous thrombosis of the arm [16], and one case-control study noted a reduced risk of venous thrombosis of the leg and pulmonary embolisms in young women [17]. On the other hand, two follow-up studies observed that participating in sports activities was associated with a small increased venous thrombosis risk [18,19]. However, in all studies data regarding type, frequency and intensity of sport were scarce, and numbers of venous thrombosis events were small. Therefore, in this study, we set out to investigate in detail whether participating in sports activities on a regular basis influences the risk of venous thrombosis.

Patients and Methods

All analyses were performed as part of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA-study), which is a large population-based case-control study. Since March 1999 until September 2004, all consecutive patients with a first venous thrombosis were recruited from six anticoagulation clinics in the Netherlands.

These clinics monitor the anticoagulant treatment of all patients within a well-defined geographical area. All patients were between 18 and 70 years of age and had their first episode of venous thrombosis in the deep veins of the leg or had a pulmonary embolism. A participant was considered ineligible when he could not read Dutch or had severe psychiatric problems. 280 Patients died before they were able to fill in a questionnaire (see below) while 82 patients were at the end stage of disease. Out of the remaining 5969 eligible patients, 5053 (84.6%) participated.



MD = missing data regarding sports activities, frequency of sports activities or body mass index
Freq SA<1 week = frequency of sports activities of less than once a week
RDD = random digit dialing controls subjects

Figure 1 Flow chart of participating patients and control subjects for inclusion in the analyses.

Partners of the participating patients were asked to serve as a control group. Those with a history of venous thrombosis were excluded. Of the participating patients, 3657 had an eligible partner of whom 2985 participated (81.6%). A second control group was collected in the same geographical area as the patients via random digit dialing, a method developed by Waksberg [20]. This method is frequently used to gather a random control group. A specific individual from the telephoned household, based on sex and age-range of the patient group, was asked to participate to avoid a selective response from healthy control subjects. In this way it was possible to obtain a random control group frequency matched for age and sex to the patients. Of the 4350 contacted eligible individuals 3000 (69%) were willing to participate. Collection of the random control group started in January 2002 and continued until December 2004. All eligible control subjects were between 18 and 70 years at time of their first contact.

Participants gave a written informed consent. This study was approved by the Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Data collection

Sports activities, frequency of performing sports, weight, standing height, surgery, plaster cast, minor injury, pregnancy, malignancy, bed rest for more than 4 consecutive days, chronic illness, hormone use and other risk factors for venous thrombosis covering a period of one year prior to the indexdate were reported in a standardized mailed questionnaire. The indexdate was the date of diagnosis of the thrombotic event for the patients and the date of filling in the questionnaire for the control subjects. Body mass index (BMI) was calculated by self-reported weight (kg) divided by height squared $(m)^2$. Minor injuries, such as sprains and small muscle ruptures, had to occur within the three months prior to indexdate. During the first months of the study, a pilot questionnaire was used. When the participant was unable to fill in the questionnaire questions were asked by phone using a standardized short version. As neither of those questionnaires contained information on regular sports activities, these individuals were excluded from the present analysis, figure 1.

Individuals who participated in sports activities at least once a week were considered to exercise. Those who participated in sports activities but with an unreported frequency or with a frequency of less than once a week were excluded, figure 1. A person was considered not to exercise when the activity he performed was not considered a sport activity. Six investigators independently scored whether an activity mentioned in the questionnaire could be considered a sport activity. An activity was considered a sports activity when it was scored as such by three or more investigators. For instance gardening, walking (not for exercise) and bowling were not considered sports activities. Activities were categorized in three different types of sport; endurance, interval, and power sports. The intensity of a specific sport was categorized according to metabolic intensity scores (METS) [21,22] into very strenuous intensity (METS≥ 8), strenuous intensity (METS≥ 6 - 8), and moderate intensity (METS≥ 3 - 6). To study whether the effect of performing sports activities had a local or systemic effect, sports activities were divided into arm and other sports. Bodybuilding, canoeing, climbing, judo, push-ups, rowing, swimming and wrestling were considered as sports mainly involving the arm, so called arm-sports. Other sports activities were categorized as other sports. We further made a distinction between gravitational sports versus non-gravitational sports. Football, volleyball, hockey, athletics, karate, Tai Kwando were considered gravitational sports, while swimming, waterpolo, hydrotherapy, aqua jogging, aqua aerobics and scuba diving were considered non-gravitational sports. Finally, based on the reported incidence density of number injuries per 1000 hours of sports activities[23], sports activities that have a high risk of injuries (more than two injuries per 1000 hours of football, volleyball, hockey, basketball, athletics, karate or Tai Kwando) were compared with sports activities with a low risk of injuries (less than one injury per 1000 hours of fitness, horse riding, swimming or aerobics).

Analysis

Odds ratios (OR) were calculated as estimates of the relative risk of thrombosis with 95% confidence intervals (CI). Odds ratios (OR_{adj}) were adjusted for sex, age and body mass index. Partners were matched to their patients to adjust for lifestyle factors resulting in 1916 eligible couples in a matched analysis (Mantel-Haenszel estimator), while all 3608 patients were contrasted to the random digit dialing controls (2336 subjects) in an unmatched

analysis, figure 1. For calculation of the overall risk we calculated a pooled odds ratio combining the odds ratio of the matched analysis with the odds ratio of the unmatched analysis. This included an adjustment for the patients who were included in both the matched and the unmatched analysis. When analyzing the risk in men and women separately only random control subjects were used, as in most couples partners were of opposite sex. Absolute risk differences were calculated using absolute risks as previously reported in a prospective study on the incidence of venous thrombosis in France [2].

To remove confounding by health status as much as possible, all participants with a malignancy were excluded, figure 1. Furthermore, we performed an analysis for the risk of idiopathic thrombosis in which only individuals were included without clinical risk factors, e.g. surgery, plaster cast, minor injury, pregnancy, malignancy, bed rest for more than 4 consecutive days or chronic illness in the year prior to indexdate. A multivariate analysis was performed among those who participated in sports activities regularly to determine whether type, frequency and intensity of sports activities were independently related to venous thrombotic risk. All analyses were performed in SAS 9.1 (SAS institute Inc, Cary, NC, USA).

Table 1. Characteristics of study population

	Patients N=3608	Control subjects N=4252
Women (%)	54.4%	53.3%
Age (5^{th} -95^{th} perc.)	47.6 (25.6-67.3)	46.6 (25.3-66.4)
BMI (kg/m^2) (5^{th} -95^{th} perc.)	27.0 (20.3-35.9)	25.5 (19.8-33.3)
Type of VT†		
PE (%)	1044 (28.9%)	
DVT leg (%)	2093 (58.0%)	
DVT leg + PE (%)	471 (13.1%)	

† PE = pulmonary embolism
DVT leg = deep venous thrombosis of the leg

Results

Overall 3608 patients and 4252 control subjects were included in the present analysis. Their characteristics are shown in table 1. Of the patients 1136 (31.4%) participated regularly in sports compared with 1686 (39.6%) control subjects. Performing sports reduced the risk of venous thrombosis (OR 0.64; 95% CI 0.58-0.71). Adjustment for sex, age and body mass index did marginally change the odds ratio (OR_{adj} 0.71; 95% CI 0.64-0.78) (table 2). The odds ratios were slightly closer to one when the partner control group was used (OR_{adj} 0.86; 95% CI 0.71-1.02) compared with using the random digit dialing control group (OR_{adj} 0.67; 95% CI 0.60-0.75).

Among participants without an injury in the preceding three months the risk of venous thrombosis was 0.7 fold decreased (OR_{adj} 0.66; 95% CI 0.59-0.74) for those who participated in sports activities compared with those who did not participate in sports activities. When the analysis was restricted to idiopathic thrombosis i.e. individuals without clinical risk factors for venous thrombosis the risk reduction was similar to the overall risk (OR_{adj} 0.67; 95% CI 0.58-0.78). Further exclusion of women receiving oral contraceptives or hormone replacement therapy did not lead to a different point estimate (OR_{adj} 0.66; 95% CI 0.54-0.79).

Table 2. Association between participating in sports activities and the risk of venous thrombosis

	Patients	Control subjects	OR (95%CI)	OR_{adj}* (95%CI)
No sport	2472 (68.6%)	2566 (60.3%)	1	1
Sports	1136 (31.4%)	1686 (39.7%)	0.64 (0.58-0.71)	0.71 (0.64-0.78)
Total	3608	4252		

*Adjusted for sex, age and body mass index
OR = odds ratio
95 % CI= 95 percent confidence interval

Among those participating regularly in sports activities, the frequency of performing a sport did not affect the risk of venous thrombosis. Different types and intensities of sports were equally beneficial (table 3).

Table 3. Relation between frequency, intensity and type of sports activities and risk of venous thrombosis

	Patients 3608	Control subjects 4252	OR_{adj}* (CI95)
No sport	2472	2566	1
Frequency			
Once per week	613	916	0.68 (0.60-0.78)
> Once per week	523	764	0.73 (0.64-0.84)
Intensity†			
Moderate intensity	374	580	0.69 (0.59-0.81)
Strenuous intensity	424	569	0.77 (0.66-0.89)
Very Strenuous intensity	334	531	0.66 (0.56-0.76)
Type of sport†			
Single type of sport(s)	808	1167	0.72 (0.64-0.81)
Only endurance sport(s)	*431*	*585*	*0.78 (0.67-0.90)*
Only interval sport(s)	*194*	*295*	*0.71 (0.58-0.87)*
Only power sport(s)	*183*	*287*	*0.62 (0.51-0.76)*
Combinations of types of sport(s)	324	513	0.67 (0.57-0.78)
Endurance and interval sport(s)	*133*	*208*	*0.73 (0.57-0.92)*
Endurance and power sport(s)	*130*	*1412*	*0.60 (0.47-0.76)*
Interval and power sport(s)	*28*	*51*	*0.58 (0.36-0.93)*
Endurance and interval and power sport(s)	*33*	*42*	*0.85 (0.52-1.36)*

*Adjusted for sex, age and body mass index.

Among those who participated in sports activities, multivariate analysis showed that frequency, intensity and type of sport were not independent determinants of venous thrombosis risk. When we compared the effect of sports that involve mainly the arm with those mainly involving the legs, we found no clear differences on the risk of deep venous thrombosis, with relative risks of 0.79 for arm sports (ORadj 0.79 95%CI 0.66-0.95) and 0.68 for other sports (ORadj 0.68 95%CI 0.61-0.76), both relative to those who did not participate in sports. Non-gravitational sports activities (0.90 95%CI 0.60-1.17) seemed to reduce the risk of venous thrombosis to a lesser extent than gravitational sports activities (0.72 95%CI 0.59-0.88) both compared with performing no sports activities. Furthermore, sports activities that had a high injury risk had a less beneficial effect on thrombotic risk (0.93 95%CI 0.69-1.26) than sports activities with a low injury risk (OR 0.70 95%CI 0.60-0.81) both compared with performing no sports activities.

Those who engaged in sports, compared with those who did not, had a 46 % reduced risk of pulmonary embolism (OR 0.54; 95% CI 0.46-0.64) and only a 24% reduced risk of deep venous thrombosis of the leg (OR 0.76; 95% CI 0.67-0.86). However, only 29% of the venous thrombosis events were isolated pulmonary embolisms, while 58% was located in the leg. When using a venous thrombosis incidence of 1.3 per 1000 person years [2], the absolute risk differences are estimated to be equal for pulmonary embolism and thrombosis of the leg (table 4).

Table 4. Relation between sport (≥ once per week) and risk of different types of venous thrombosis

	Sport		Odds ratio* (95% CI)	Absolute risk		Absolute risk difference
	yes	no		Sport	No sport	
Control subjects	1563	2566	1 (ref)			
PE†	287	757	0.54 (0.46-0.64)	0.25/1000	0.44/1000	0.20/1000
DVT leg†	696	1397	0.76 (0.67-0.86)	0.63/1000	0.83/1000	0.20/1000
DVT leg† + PE†	153	318	0.79 (0.63-0.98)	0.15/1000	0.19/1000	0.04/1000

*Adjusted for sex, age and body mass index

The effect of performing sports seemed slightly different in men and women. In men the risk reduction was 22% (OR_{adj} 0.78; 95% CI 0.66-0.93), while the 39% risk reduction was more pronounced in women (OR_{adj} 0.61; 95% CI 0.52-0.70). Exclusion of women receiving oral contraceptives, hormone replacement therapy and those who were pregnant led to a risk reduction of 55% (OR_{adj} 0.45; 95% CI 0.36-0.57). No differences in odds ratios were found for the different age groups; participants aged 18-39 had an OR_{adj} of 0.71 (95% CI 0.59-0.86), those aged 40-59 had an OR_{adj} of 0.70 (95% CI 0.61-0.81) and those between 60 and 70 years had an OR_{adj} of 0.68 (95% CI 0.52-0.89), all odds ratios compared with those who did not engage in sports. As the risk of venous thrombosis increases with age [2], the absolute risk reduction of venous thrombosis associated with sports activities was higher in old compared with young individuals. For example, if all elderly individuals would exercise, approximately 1.9 per 1000 individuals would get a venous thrombosis on a yearly basis while if all individuals in this age group would not exercise this number would be 2.8 per 1000 individuals per years. As these numbers are 0.2 per 1000 and 0.3 for those aged 18 to 39, the risk benefit that could be obtained in the elderly would be much larger (figure 2).

High body mass index (BMI) increases the risk of venous thrombosis and is associated with a lower participation in sports activities; therefore the effect of both was studied simultaneously. Compared with those who did participate in sports activities and were lean (BMI <25 kg/m^2) lean individuals who did not participate in sports activities had a 1.7-fold increased venous thrombosis risk (OR_{adj} 1.71 95% CI 1.46-1.99). Among those participating in sports activities, being obese (BMI > 30 kg/m^2) resulted in a 3.3-fold (OR_{adj} 3.26 95% CI 2.42-4.39) increased risk compared with being lean (BMI < 25 kg/m^2). Obese participants who did not participate in sports activities had a 4.2-fold increased risk relative to lean individuals who participated in sports activities (OR_{adj} 4.21 95% CI 3.44-5.16).

Discussion

Individuals who participate in sports activities on a regular basis have a lower risk of developing a deep venous thrombosis of the leg and pulmonary embolism compared with those who do not participate in sports activities. Risk reductions were similar in various types, frequencies and intensities of sports.

In a joint database of two large cohort studies, i.e. the Atherosclerosis' Risk In Community (ARIC) and the Cardiovascular Health Study (CHS) a small increased risk to a null effect was found for the association of physical activity and venous thrombosis risk [19]. The analysis was based on 215 individuals who developed their first venous thrombotic event during follow-up, which might have been too few to observe an effect. Another cohort study, the Physicians Health Study with 358 venous thrombosis events, also showed a small increased risk of venous thrombosis with increasing frequency of exercise compared with those who did not exercise at all. Both studies did not provide an explanation for this increased risk. In contrast, as in our study, a case-control study including 196 patients showed a decreased venous thrombosis risk for young physical active women [17]. A difference between these cohort studies and the case-control studies is that in case-control studies patients reported their prior sports activities shortly after the venous thrombotic event. In the follow-up studies, leisure time physical activity data were assessed at baseline. As the median follow-up time was eight to thirteen years, physical activity at baseline may not have accurately reflected physical activity prior to the event. Secondly, both cohort studies studied the risk mainly among the elderly as most patients were over 65 years of age when they had their venous thrombosis. Both case-control studies included individuals with a mean age of 48 and 35 years, resulting in a more than 20 year age difference for the cohort and case-control studies. A third reason for this difference between the results obtained in the case-control and cohort studies might be recall bias, since in case-control studies participants are interviewed after the event. Since cases and partner controls filled in the questionnaire simultaneously, we do not believe recall bias very likely.

We found slight differences between the analyses which only included the partners of cases and which only included the random digit controls. Couples often have similar lifestyles and therefore similar sports activities. We performed a matched analysis that takes this association into account. As this matched analysis also accounts for other, unmeasured, confounders, this might explain why this risk estimates was closer to one compared with the unmatched analysis using the random digit dialing control subjects. However, it is important to note that both analyses yielded beneficial effects of sports activities. Population studies on sports activities in the Netherlands showed that between 48 and 52%

of the population performs one or more sports regularly [24]. This is equal to the percentage in our random control group (44%).

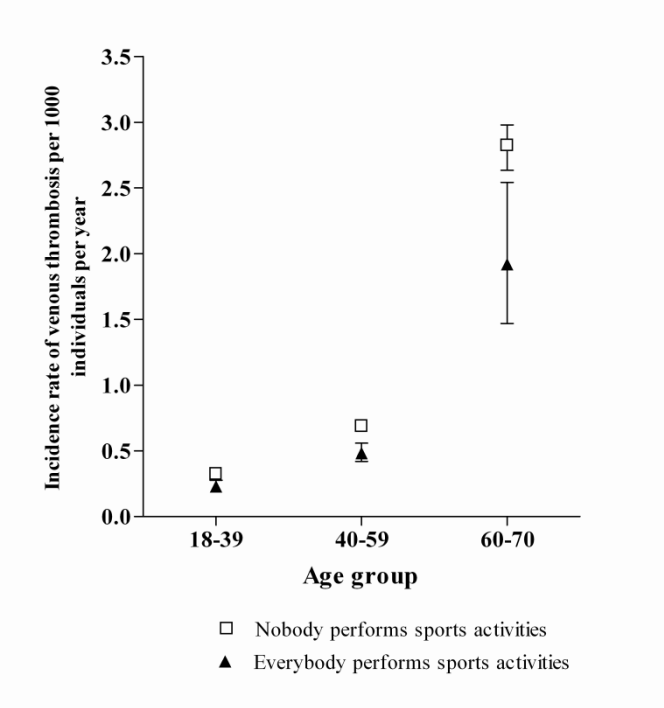


Figure 2 Theoretical number of new cases of venous thrombosis per year if all participants would or would not participate in sports activities

Previously we reported that sports activities involving the legs reduced the risk of venous thrombosis of the arm (systemic effect), whereas sports activities involving the arms increased the risk of venous thrombosis in the arms, which was most striking for thrombosis in the right arm, which most often is the dominant arm used in sports. This suggests systemic and local effects, probably due to a compression of the arm veins [16]. Such differences were not clear for deep vein thrombosis of the leg. A systemic reduction in venous thrombosis risk could be caused by alterations in plasma coagulation factors. Although not all studies have shown to be consistent, decreased levels of both fibrinogen and factor VIII after exercise have been observed [11-14,25]. High levels of fibrinogen, and factor VIII have been shown to increase the risk of venous thrombosis [26,27].

We did not find a dose-response relationship between intensity, frequency and duration of sports activities and risk of thrombosis. It may well be that the beneficial effect is conferred by any engagement in sports, and not further influenced by more frequent of intense engagement. It is also possible that minor injuries play a role in offsetting the beneficial effect. Intense and frequent participation in sports activities results in a high risk of injuries [28] and these may cause venous thrombosis [29]. We found some support for this notion, since participation in sports activities with a high injury risk yielded less benefit than sports activities with a low injury risk.

A potential problem when analyzing the association between sport and disease is that the risk reduction, which appears to have been caused by sports activities, may actually be caused by a reduction in weight or body mass index. Although some believe that physical inactivity is a single cause of cardiovascular diseases and not a high body mass index [10,30]. To ensure that our results were independent of the effect of obesity we adjusted all analyses for body mass index. To study whether body mass index and sports activities have a joint effect we performed a multivariate analysis. Our results show that a high body mass index and not participating in sports activities each individually increase the risk of venous thrombosis, and that the combination of obesity with inactivity leads to the highest risk.

Besides possible confounding by body mass index, the health status of an individual might affect both the risk of venous thrombosis and participation in sports activities. We tried to limit confounding by health status as much as possible by excluding all participants with malignancy. Furthermore we performed an analysis for the risk of idiopathic venous thrombosis, thereby excluding all individuals with known risk factors for disease. The estimate obtained in this analysis was not different from the overall estimate. Although residual confounding by health status might be present, the absence of any effect of these restricted analyses makes us confident that the observed relation between sporting activities and venous thrombosis is causal.

Overall, participating in sports activities on a regular basis decreases the risk of venous thrombosis. All the various types, intensities and frequencies of sports activities decrease the risk to a similar level.

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References

1. Nördstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med 1992; 232: 155-60.
2. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000; 83: 657-60.
3. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353: 1167-73.
4. Virchow, R. Phlogose und Thrombose im Gefässystem. Staatsdruckerei, 1856.
5. Simpson K. Shelter deaths from pulmonary embolism. Lancet 1945; 744.
6. Laursen SB, Jensen TN, Bolwig T, Olsen NV. Deep venous thrombosis and pulmonary embolism following physical restraint. Acta Psychiatr Scand 2005; 111: 324-7.
7. Beasley R, Raymond N, Hill S, Nowitz M, Hughes R. eThrombosis: the 21st century variant of venous thromboembolism associated with immobility. Eur Respir J 2003; 21: 374-6.
8. El Sayed MS. Effects of exercise on blood coagulation, fibrinolysis and platelet aggregation. Sports Med 1996; 22: 282-98.
9. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004; 351: 2694-703.
10. Wessel TR, Arant CB, Olson MB, Johnson BD, Reis SE, Sharaf BL, Shaw LJ, Handberg E, Sopko G, Kelsey SF, Pepine CJ, Merz NB. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA 2004; 292: 1179-87.
11. Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. Circulation 2002; 105: 1785-90.
12. El Sayed MS, Lin X, Rattu AJ. Blood coagulation and fibrinolysis at rest and in response to maximal exercise before and after a physical conditioning programme. Blood Coagul Fibrinolysis 1995; 6: 747-52.

13. Hilberg T, Nowacki PE, Muller-Berghaus G, Gabriel HH. Changes in blood coagulation and fibrinolysis associated with maximal exercise and physical conditioning in women taking low dose oral contraceptives. J Sci Med Sport 2000; 3: 383-90.
14. Ponjee GA, Janssen GM, van Wersch JW. Prolonged endurance exercise and blood coagulation: a 9 month prospective study. Blood Coagul Fibrinolysis 1993; 4: 21-5.
15. Burg van den PJ, Hospers JE, van Vliet M, Mosterd WL, Bouma BN, Huisveld IA. Effect of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men. J Appl Physiol 1997; 82: 613-20.
16. van Stralen KJ, Blom JW, Doggen CJM, Rosendaal FR. Strenuous sport activities involving the upper extremities increase the risk of venous thrombosis of the arm. J Thromb Haemost 2005; 3: 2110-1.
17. 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.
18. 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.
19. 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.
20. Waksberg J. Sampling Methods for Random Digit Dialing. J Am Stat Assoc 1978; 73: 40-6.
21. Ainsworth BE, Haskell WL, Leon AS, Jacobs Jr. DR, Montoye HJ, Sallis JF, Paffenbarger Jr. RS. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993; 25: 71-80.
22. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett Jr. DR, Schmitz KH, Emplaincourt PO, Jacobs Jr. DR, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000; 32: S498-S504.
23. Vriend I, van Kamper B, Schmikli S, Eckhardt J, Schoots W, den Hertog P. Ongevallen en Bewegen in Nederland 2000-2003: Ongevalsletsels en sportblessures in kaart gebracht. 2005.
24. Sociaal cultureel planbureau. Rapportage sport. 2003.
25. Yarnell JW, Sweetnam PM, Rumley A, Lowe GD. Lifestyle factors and coagulation activation markers: the Caerphilly Study. Blood Coagul Fibrinolysis 2001; 12: 721-8.
26. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briët E, Vandenbroucke JP. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms--the Leiden Thrombophilia Study (LETS). Thromb Haemost 1994; 71: 719-22.
27. Koster T, Blann AD, Briët E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet 1995; 345: 152-5.
28. Jones BH, Cowan DN, Knapik JJ. Exercise, training and injuries. Sports Med 1994; 18: 202-14.
29. Knudson MM, Ikossi DG. Venous thromboembolism after trauma. Curr Opin Crit Care 2004; 10: 539--48.
30. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. Am J Clin Nutr 1999; 69: 373-80.
31. Kauermann G, Carroll RJ. A note on the efficiency of sandwich covariance matrix estimation. J Am Stat Assoc 2001; 96: 1387-96.