Physical activity and risk of venous thromboembolism. The Tromsø study

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ABSTRACT

Background
Previous studies have shown differences in the impact of regular physical exercise on the risk of venous thromboembolism. The inconsistent findings may have depended on differences in study design and specific population cohorts (men only, women only and elderly). We conducted a prospective, population-based cohort to investigate the impact of regular physical exercise on the risk of venous thromboembolism.

Design and Methods
Risk factors, including self-reported moderate intensity physical exercise during leisure time, were recorded for 26,490 people aged 25-97 years old, who participated in a population health survey, the Tromsø study, in 1994-95. Incident venous thromboembolic events were registered during the follow-up until September 1, 2007.

Results
There were 460 validated incident venous thromboembolic events (1.61 per 1000 person-years) during a median of 12.5 years of follow-up. Age, body mass index, the proportion of daily smokers, total cholesterol, and serum triglycerides decreased (P<0.001), whereas high density cholesterol increased (P<0.001) across categories of more physical exercise. Regular physical exercise of moderate to high intensity during leisure time did not significantly affect the risk of venous thromboembolism in the general population. However, compared to inactivity, high amounts of physical exercise (≥3 hours/week) tended to increase the risk of provoked venous thromboembolism (multivariable hazard ratio, 1.30; 95% confidence interval, 0.84-2.0), and total venous thromboembolism in the elderly (multivariable hazard ratio, 1.33; 95% confidence interval, 0.80-2.21) and in the obese (multivariable hazard ratio, 1.49; 95% confidence interval, 0.63-3.50). Contrariwise, compared to inactivity, moderate physical activity (1.0-2.9 hours/week) was associated with a border-line significant decreased risk of venous thromboembolism among subjects under 60 years old (multivariable hazard ratio, 0.72; 95% confidence interval, 0.48-1.08) and subjects with a body mass index of less than 25 kg/m^2 (multivariable hazard ratio, 0.59; 95% confidence interval, 0.35-1.01).

Conclusions
Our study showed that regular, moderate intensity physical exercise did not have a significant impact on the risk of venous thromboembolism in a general population. Future studies are required to assess the impact of regular physical exercise on venous thromboembolism risk in different population subgroups.

Key words: venous thromboembolism, physical exercise, general population.

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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a common multifactorial disease, with serious short- and long-term complications, and a potential fatal outcome.[1,2] The annual incidence is approximately 1-3 cases per 1,000 adults in developed countries,[3,4] and VTE is the third most common cardiovascular disease.[5,6] Clinical risk factors such as hospitalization, malignancy, trauma, surgery, congestive heart failure, estrogen supplementation, and central venous lines account for the majority of VTE events, but 25%-50% have no predisposing risk factors.[3,7,8] Thus, it is pivotal to identify modifiable risk factors for VTE, to identify individuals at risk, and to alter exposure in order to prevent the disease.

Already in the mid 19th century, Virchow affirmed that blood stasis is a major contributor to venous thrombosis,[9] and conditions in which venous stasis occurs, such as temporary immobilization and physical restriction, are associated with increased risk of VTE.[10-12] Muscle activity of the lower limbs promotes an acute and substantial decrease in venous pressure, elevation of venous flow, and prevention of edema.[13-15] It is, therefore, reasonable to assume that regular physical exercise protects against VTE. However, information on the impact of physical exercise on the incidence of VTE is scarce and unclear.

In a large population-based case-control study of 7,860 subjects aged 18-70 years, participation in regular sport activities at least once a week was associated with a 29% reduced risk of VTE [odds ratio (OR), 0.71; 95% confidence interval (95% CI), 0.64-0.78].[16] Similarly, regular physical activity or vigorous activity once or more a week protected young women (15-44 years of age) against VTE in another case-control study.[17] In a prospective cohort study of 29,000 Swedish women (25-67 years old), strenuously exercising women (bicycling, gymnastics/dancing more than once a week) had half the risk of VTE compared to that of sedentary women, whereas walking several times a week did not have a significant protective effect.[18] The Physicians' Health Study reported an increased risk of VTE associated with regular exercise in men (40-84 years old), particularly for provoked events (hazard ratio, 1.19; 95% CI, 1.06-1.34 per one category of exercise).[5] Similarly, a longitudinal study among 5,500 elderly (≥65 years of age) men and women found a 1.75-fold higher risk in subjects undertaking strenuous exercise compared to that in the non-exercising group.[19] The study also found that mild-intensity exercise (walking) was associated with a non-significant decrease in the risk of incident VTE (hazard ratio, 0.75; 95% CI: 0.49-1.16).[19] Finally, in the Longitudinal Investigation of Thromboembolism Etiology (LITE) study among 19,293 American men and women ≥45 years of age, with 215 VTE events during an 8-year follow-up, no significant association was found between incident VTE and physical activity, even though there was a tendency for increased risk with increasing levels of activity.[20]

The apparent contrasting impact of physical exercise on the risk of VTE in previous studies may be explained by differences in study design (e.g. case-control and prospective cohorts), study populations (e.g. gender specific studies, middle-aged and elderly populations), definitions of physical activity, and rather limited number of VTE events. We, therefore, found it pertinent to investigate the association between physical exercise and risk of VTE in a large prospective cohort study of a general population.

Design and Methods

Study population

Participants were recruited from the fourth survey of the Tromsø study conducted in 1994-95, a single-center, prospective, population-based study, with repeated health surveys of inhabitants in Tromsø, Norway. All inhabitants aged 25 years old or over were invited, and 27,158 participated (77% of the population invited). Data were collected by physical examination, blood samples, and self-administered questionnaires. The study was approved by the regional committee for research ethics, and all participants gave their informed, written consent. Incident VTE events among the study participants were recorded from the date of enrollment through to the end of follow-up, September 1, 2007. Subjects who did not consent to medical research (n=300) and subjects not officially registered inhabitants of the municipality of Tromsø (n=43) were excluded from the study. Furthermore, subjects for whom information on physical exercise of moderate and higher intensity during leisure time was missing (n=278) were excluded. Among the subjects with a VTE-event during follow-up, 47 were found to have had an event prior to inclusion in 1994-95, and these subjects were excluded. Overall, 26,490 subjects were included in our study.

Baseline measurements

Height and weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms, divided by the square of height in meters (kg/m^2). Information on the amount of moderate and high intensity physical activity (vigorous enough to work up a sweat and cause shortness of breath) carried out during leisure time per week during the previous year was collected by a self-administered questionnaire. Subjects were asked to estimate the average amount of such activity in leisure time per week in the following categories; 0 h, 0.1-0.9 h, 1-2.9 h and 3 h or more. Information on self-reported diabetes, current smoking (pipe/cigar/cigarettes), current hormone therapy use and prior cardiovascular disease (myocardial infarction, angina pectoris or stroke) was also collected through a self-administered questionnaire. Hormone therapy was defined as self-reported current use of estrogen supplementation or current use of oral contraceptives. The information on self-reported diabetes was supplemented by searching the hospital discharge diagnosis registry at the University Hospital of North Norway for a diagnosis of diabetes in participants prior to baseline. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846, Critikon Inc, Tampa, FL, USA) by trained personnel. Participants rested for 2 minutes in a sitting position, and then three readings were taken, separated by 2-minute intervals, on the upper right arm. The average of the last two readings was used in the analyses. Non-fasting blood samples were collected from an antecubital vein; serum was prepared by centrifugation after 1 h of rest at room temperature, and then analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol was analyzed by the CHOD-PAP method (Boehringer Mannheim, Germany), and serum high-density lipoprotein-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride.

Identification and validation of venous thromboembolism

All first lifetime events of VTE during the follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology registry at the University Hospital of North Norway, from the date of enrollment in the Tromsø study (1994-95), through to September 1, 2007. The University Hospital of North Norway is the only hospital in the region, and all hospital care and relevant diagnostic radiology in the Tromsø community is pro-

vided exclusively by this hospital. The relevant discharge codes were ICD-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9 for the period 1994-1998 and ICD-10 codes I80.0-I80.3, I80.8, I80.9, I81, I82.0-I82.3, I82.8, I82.9, I67.6, O22.3, O22.5, O87.1, O87.3, I26.0 and I26.9 for the period 1999-2007. The hospital discharge diagnosis registry included both outpatient clinic visits and hospital admissions. An additional search through the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE, either as a cause of death, or as a significant condition, were identified. We also searched the radiology database, in order to identify potential cases of objectively confirmed VTE that may have been missed because of coding errors in the index of medical diagnoses. All relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during the 13-year period were systematically reviewed by trained personnel and cases with objectively confirmed VTE were identified.

The medical records for each potential VTE-case, derived from the hospital discharge diagnosis registry, the autopsy registry, or the radiology registry, were reviewed by trained personnel. For subjects identified from the hospital discharge diagnosis registry and the radiology procedure register, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled: (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography or autopsy); (ii) the medical record indicated that a physician had made a diagnosis of deep vein thrombosis or pulmonary embolism; (iii) signs and symptoms consistent with deep vein thrombosis or pulmonary embolism were present; and (iv) the patient underwent therapy with anticoagulants (heparin, warfarin, or a similar agent), thrombolytics, or vascular surgery. For subjects identified from the autopsy register, a VTE event was recorded as an outcome when the autopsy record indicated VTE as the cause of death or as a significant condition.

Based on the presence of provoking factors at the time of diagnosis, the VTE event was classified as unprovoked (no provoking factors) or provoked (one or more provoking factors). Major surgery, trauma, or an acute medical condition (acute myocardial infarction, ischemic stroke or major infectious disease) within 8 weeks prior to event, active cancer at the time of the event, marked immobilization (bed rest for longer than 3 days, confinement to a wheelchair or long distance travel exceeding 4 h within the 14 days prior to the event) were considered provoking factors.

Statistical analyses

For each participant, person-years of follow-up were accrued from the date of enrollment in 1994-95, through to the date a VTE event was first diagnosed, the date the participant died or moved from the municipality of Tromsø, or through to the end of the study period on September 1, 2007. Information on death and migration were obtained from the National Population Register of Norway, and subjects who died (n=2,995) or moved from the municipality of Tromsø (n=3,706) during follow-up were censored.

Analysis of covariance and logistic regression was used in age-adjustments of continuous and dichotomous baseline characteristics, respectively. Logistic and multiple regression models were used in trend analysis of cardiovascular risk factors at baseline. Crude incidence rates were calculated as the number of events per 1,000 person-years, and the 95% CI for the incidence rate was calculated using the formulae: lower CI-limit = incidence rate/$e^{(1.96/\sqrt{\text{Number of events}})}$ and upper CI-limit= incidence rate x $e^{(1.96/\sqrt{\text{Number of events}})}$. Cox-proportional hazard regression models were used to estimate age-adjusted and multivariable-adjusted hazard ratios, with 95% CI for VTE. In the multivariable model, hazard ratios were adjusted for age, BMI, current smoking, self-reported diabetes and hormone therapy (women only). Statistical interactions between strenuous exercise and age, or gender, were assessed by including cross product terms in the proportional hazard models. None of the assessed product terms was statistically significant. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for categories of strenuous physical activity. Gender-specific hazard ratios for total VTE events were calculated for various levels of strenuous physical activity, whereas non-gender-specific analysis was performed when assessing the risk of unprovoked and provoked VTE due to the low number of events in the separate categories. Hazard ratios for total VTE events were also estimated separately for age groups (<60 years and ≥60 years) and BMI categories and with provoked or unprovoked VTE events as end-points. Statistical analyses were carried out using the SPSS version 15.0 (SPSS Inc. Chicago, IL, USA). The level of statistical significance was 0.05.

Results

There were 460 validated incident VTE events registered during 286,467 person-years (median 12.5 years) of follow-up. The overall crude incidence of VTE was 1.61 per 1000 person-years. The characteristics of patients who had VTE at the time of the event are shown in Table 1. Sixty-four percent had deep vein thrombosis and 36% had pulmonary embolism with or without concurrent deep vein thrombosis. Overall, 191 (42%) VTE events were classified as unprovoked. Cancer was the most common provoking factor, and 23% of the VTE patients had active cancer when VTE was diagnosed. The proportion of incident provoked VTE, incident deep vein thromboses and pulmonary emboli, and the distribution of clinical risk factors and provoking factors were similar among women and men (Table 1).

Traditional cardiovascular risk factors across categories of self-reported physical exercise during leisure time stratified

Table 1. Characteristics of VTE events (n=460). The Tromsø study 1994-2007.

	Women (n=243)	Men (n=217)	Total (n=460)
Deep vein thrombosis (%)	65.0 (158)	63.1 (137)	64.1 (295)
Pulmonary embolism (%)	35.0 (85)	36.9 (80)	35.9 (165)
Unprovoked	41.6 (101)	41.4 (90)	41.5 (191)
Clinical risk factors			
Estrogens[a]	14.4 (35)	–	–
Pregnancy/puerperium	1.2 (3)	–	–
Heredity[b]	3.7 (9)	1.8 (4)	2.8 (13)
Other medical conditions[c]	24.7 (60)	18.4 (40)	21.7 (100)
Provoking factors			
Surgery	17.7 (43)	16.6 (36)	17.2 (79)
Trauma	7.4 (18)	6.0 (13)	6.7 (31)
Acute medical conditions	13.6 (33)	17.1 (37)	15.2 (70)
Cancer	23.9 (58)	22.1 (48)	23.0 (106)
Immobilization[d]	18.9 (46)	19.4 (42)	19.1 (88)
Other[e]	3.3 (8)	5.1 (11)	4.1 (19)

Values are percentages, with numbers in brackets. Some patients had more than one provoking factor at the time of the event. [a]Estrogens = hormone replacement therapy or oral contraceptives. [b]VTE-event in one or more first-degree relatives prior to the age of 60 years. [c]Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders). [d]Immobilization = bed rest >3 days, wheelchair, cast, air/automobile travel >4 h in the 14 days prior to the event. [e]Other provoking factors described by a physician in the medical record (e.g. intravascular catheter).

by gender and adjusted for age at baseline (1994-95) are shown in Table 2. Age, the frequency of smokers, and proportion of the population without cardiovascular diseases declined linearly with increasing physical exercise in both men and women. As expected, BMI, and total cholesterol and triglyceride levels declined, whereas high-density lipoprotein cholesterol concentration increased in both genders with increasing physical exercise. In women, systolic blood pressure decreased with increased physical exercise, whereas the frequency of diabetes mellitus was unaltered across categories of physical exercise. In men, the frequency of diabetes mellitus decreased with higher levels of physical exercise, whereas systolic blood pressure was no different.

Gender-stratified multivariable hazard ratios for total VTE across categories of average time spent on physical exercise during leisure time (0 h, 0.1-1 h, 1-2.9 h, and ≥3 h) did not show any significant gender differences (*data not shown*).

Incidence rates of total VTE, provoked VTE and unprovoked VTE across categories of physical exercise are shown in Table 3. The incidence rates of total VTE, provoked VTE and unprovoked VTE declined with increasing physical exercise. This apparent beneficial effect of physical exercise was mostly dependent on age differences between categories of physical exercise as the effect disappeared after adjustment for age (*data not shown*). In multivariable analysis adjusted for age, gender, BMI, diabetes, smoking and hormone therapy (women only), moderate amounts of physical exercise (0.1-2.9 h per week) were associated with modest non-significant decreases in the risk of total VTE, provoked VTE and unprovoked VTE with a subsequent increased risk of VTE among subjects who reported more than 3 h of physical exercise per week (Table 3). Subjects who reported more than 3 h exercise per week had a multivariable hazard ratio of 1.13 (95% CI, 0.80-1.61) for total VTE and 1.30 (95% CI, 0.84-2.01) for provoked VTE compared to inactive participants.

To further investigate whether the risk of total VTE was affected by physical exercise in subgroups, stratified analyses were conducted for age, BMI, and type of VTE (deep vein thrombosis or pulmonary embolism) (Table 4). In general, the results showed a similar pattern across all subgroups with lower hazard ratios for total VTE in subjects performing moderate exercise (0.1-2.9 h per week) and increased hazard ratios for those carrying out more physical activity (≥3 h per week). However, the increased risk of total VTE associated with high physical activity (≥3 h per week) was more pronounced among the elderly (≥60 years of age) and obese (BMI ≥30.0 kg/m^2), whereas younger subjects (<60 years of age) and subjects with normal body composition (BMI<25.0 kg/m^2) did not show an increased risk of VTE compared to the risk in inactive subjects (Table 4).

Table 2. Cardiovascular risk factors, stratified by gender, across categories of average time spent on physical exercise of moderate to high intensity during leisure time at baseline (age-adjusted). The Tromsø study 1994-2007.

	Strenuous Physical Exercise (hours per week)			
	0	0.1-2.9	≥ 3	*P* for trend
Women (n=13892)				
Numbers	7881	5147	864	-
Age (years)	52.0 (16.3)	40.7 (11.6)	40.4 (12.5)	<0.001
BMI (kg/m^2)	25.0 (4.5)	24.6 (3.8)	24.1 (3.5)	<0.001
Total cholesterol (mmol/L)	6.12 (1.43)	5.96 (1.2)	5.89 (1.19)	<0.001
Triglycerides (mmol/L)	1.41 (0.96)	1.29 (0.76)	1.20 (0.62)	<0.00
HDL-cholesterol (mmol/L)	1.62 (0.41)	1.66 (0.39)	1.74 (0.41)	<0.001
Systolic blood pressure (mmHg)	133 (24.8)	132 (17.7)	132 (16.9)	0.004
Smoking (%)	40.0 (2986)	31.6 (1815)	24.3 (257)	<0.001
Diabetes (%)	1.2 (217)	1.1 (57)	1.1 (7)	0.764
Cardiovascular disease (%)†	2.2 (648)	1.3 (72)	0.8 (11)	<0.001
Hormone therapy (%)	11.1(859)	12.7 (724)	14.5 (164)	<0.001
Men (n=12598)				
Numbers	5197	5560	1841	-
Age (years)	51.9 (15.4)	43.1 (12.3)	41.9 (12.7)	<0.001
BMI (kg/m^2)	25.7 (3.6)	25.6 (3.19)	25.3 (2.9)	<0.001
Total cholesterol (mmol/L)	6.13 (1.24)	6.02 (1.18)	5.88 (1.19)	<0.001
Triglycerides (mmol/L)	1.86 (1.77)	1.76 (1.18)	1.62 (1.17)	<0.001
HDL-cholesterol (mmol/L)	1.32 (0.36)	1.35 (0.33)	1.41 (0.37)	<0.001
Systolic blood pressure (mmHg)	137 (19.4)	138 (15.8)	137 (15.1)	0.828
Smoking (%)	43.8 (2238)	34.9 (1886)	26.8 (584)	<0.001
Diabetes (%)	1.6 (162)	1.2 (62)	0.9 (21)	0.005
Cardiovascular disease (%)†	5.5 (749)	3.4 (214)	2.1 (64)	<0.001

Values are means ± SD, or percentages with numbers in brackets. †History of myocardial infarction, angina pectoris or cerebrovascular accident.

Discussion

The purpose of the current study was to investigate the association between moderate to high intensity physical

Table 3. Incidence rates (IR) and hazard ratios (HR) with 95% confidence interval (CI) of venous thromboembolism (VTE) by levels of strenuous physical exercise during leisure time per week for people participating in the Tromsø study 1994-2007.

	Person-years	Events	IR	Multivariable HR (95%CI)*
Total VTE (n=460)				
0 hours	138691	304	2.19	Ref.
0-0.9 hours	59567	63	1.06	0.88 (0.66-1.17)
1-2.9 hours	58436	53	0.91	0.82 (0.60-1.11)
≥ 3 hours	29773	40	1.34	1.13 (0.80-1.61)
P for trend				0.791
Provoked VTE (n=269)				
0 hours	137819	178	1.29	Ref.
0-0.9 hours	59378	36	0.61	0.91 (0.63-1.32)
1-2.9 hours	58277	29	0.50	0.81 (0.54-1.22)
≥ 3 hours	29655	26	0.88	1.30 (0.84-2.01)
P for trend				0.805
Unprovoked VTE (n=191)				
0 hours	137496	126	0.92	Ref.
0-0.9 hours	59305	27	0.46	0.85 (0.55-1.31)
1-2.9 hours	58224	24	0.41	0.84 (0.53-1.32)
≥ 3 hours	29584	14	0.47	0.93 (0.53-1.65)
P for trend				0.508

*IR: Crude incidence rate per 1000 person-years. *Multivariable model adjusted for the following covariates at baseline; age, gender, BMI, diabetes, smoking, with inactive subjects as the reference group.*

exercise during leisure time and risk of VTE in a large prospective cohort study in a general population. A higher degree of activity assessed by self-reported physical exercise was associated with a favorable cardiovascular risk profile in both men and women. Overall, no significant association was found between level of physical activity and risk of VTE, but moderate activity (0.1-2.9 h/week) tended to reduce the risk of VTE, whereas higher activity (≥3 h/week) was associated with a non-significant increased risk of VTE. Subanalyses showed that intense physical activity (≥3 h/week) was associated with increased risk estimates for VTE especially among the elderly and obese.

Table 4. Hazard ratios (HR) of total VTE by levels of strenuous exercise during leisure time per week for subjects stratified by age, BMI and type of VTE. The Tromsø study 1994-2007.

Subgroups	Exercise level	Subjects at risk	Events	Multivariable HR (95%CI)*
Age (years)				
<60	0 hours	8683	108	Ref
	0-0.9 hours	4886	42	0.86 (0.60-1.24)
	1-2.9 hours	4785	32	0.72 (0.48-1.08)
	≥ 3 hours	2422	22	0.99 (0.62-1.59)
	P for trend			0.356
≥60	0 hours	4395	196	Ref
	0-0.9 hours	541	21	0.87 (0.55-1.36)
	1-2.9 hours	495	21	0.98 (0.61-1.55)
	≥ 3 hours	283	18	1.33 (0.80-2.21)
	P for trend			0.541
BMI (kg/m^2)				
<25.0	0 hours	6413	93	Ref
	0-0.9 hours	2911	25	0.91 (0.57-1.44)
	1-2.9 hours	3066	17	0.59 (0.35-1.01)
	≥ 3 hours	1563	13	0.85 (0.46-1.56)
	P for trend			0.152
25.0-29.9	0 hours	4890	140	Ref
	0-0.9 hours	1988	27	0.86 (0.56-1.31)
	1-2.9 hours	1846	26	0.89 (0.58-1.39)
	≥ 3 hours	976	20	1.26 (0.77-2.05)
	P for trend			0.739
≥30.0	0 hours	1731	71	Ref
	0-0.9 hours	526	11	0.87 (0.45-1.67)
	1-2.9 hours	364	10	1.24 (0.62-2.48)
	≥ 3 hours	163	6	1.49 (0.63-3.50)
	P for trend			0.391
Type of VTE				
DVT	0 hours	12970	196	Ref
	0-0.9 hours	5406	42	0.90 (0.64-1.27)
	1-2.9 hours	5258	31	0.73 (0.49-1.08)
	≥ 3 hours	2691	26	1.12 (0.72-1.72)
	P for trend			0.581
PE	0hrs	12882	108	Ref
	0-0.9 hours	5385	21	0.85 (0.52-1.37)
	1-2.9 hours	5249	22	0.99 (0.61-1.61)
	≥ 3 hours	2679	14	1.18 (0.66-2.11)
	P for trend			0.753

**Multivariable model adjusted for the following covariates at baseline; age, gender, BMI, diabetes, smoking and hormone therapy with inactive subjects as the reference group. DVT: deep vein thrombosis; PE: pulmonary embolism.*

In our study, the incidence rates for total VTE, provoked VTE and unprovoked VTE decreased significantly across categories of physical exercise during leisure time. Self-reported physical exercise was strongly associated with age, BMI, lipid profile, and the presence of diabetes mellitus and cardiovascular diseases. The association between physical exercise and risk of VTE disappeared after adjustment for potential confounders such as age alone, and further adjustment for gender, BMI, diabetes, smoking and hormone therapy (women only). In agreement with data from the LITE–study, which included middle-aged and elderly subjects from a general population,[20] physical exercise was not found to be an independent predictor of future risk of VTE in our study. However, previous gender-specific cohort studies found apparent opposite effects of physical exercise on risk of VTE, protecting against VTE in a population of middle-aged Swedish women (the MISS study)[18] and moderately increasing the risk in middle-aged and elderly male physicians.[5] In our study, similar risk estimates were found for women and men in gender-stratified analyses across categories of physical exercise. Thus, it is unlikely that different outcomes in the gender-specific cohorts are mediated by gender-specific actions of physical exercise on risk of VTE, time spent on physical exercise per week, or differences in exercise intensity.

Recently, the risk of future VTE was reported to decline transiently with low energy expenditure and intensity exercise with a subsequent elevation in risk with increasing intensity and greater energy expenditure associated with exercise in a cohort study among elderly (≥65 years of age).[19] In accordance with this, we observed a non-significant decreased risk of VTE in subjects spending less than 3 h per week on physical exercise of moderate to high intensity. The protective effect seemed most pronounced among young (<60 years) and lean (BMI<25kg/m^2) subjects. The risk estimates for VTE increased in elderly (≥60 years of age) who reported more than 3 h exercise per week (Table 4). Our subanalyses also revealed that high physical activity had an adverse effect on the risk of VTE in obese individuals.

Information about exercise habits was obtained by different questionnaires without registration of the individual physical performance status in all studies assessing the risk of VTE by physical exercise[5,16-20] In case-control studies, cases provided information on exercise habits after the VTE event, whereas exercise habits are supposed to be registered before the VTE events in cohort studies. Even though the case-control studies ascertained exercise habits for the period prior to the VTE event,[16,17] there is a risk of recall bias. It is possible that the cases' knowledge of the disease, and the time since the event occurred, would affect self-reported exercise habits. In one apparent prospective cohort study (the MISS study),[18] exercise habits were registered at the end of the 12-year observation period. It is possible that the VTE event imposed changes in exercise habits (e.g. 20-60% of DVT patients develop post-thrombotic syndrome[21]) at the time of registration. Thus, it is a distinct feature that case-control[16,17] and cohort[18] studies with a retrospective registration of exercise habits showed a strong beneficial

impact of physical exercise on risk of VTE, whereas actual cohort studies either showed that physical exercise had no effect[20] or increased the risk of VTE.[5,19] The distinct difference in effect of physical exercise on risk of VTE, due to the sequence with which information on exercise habits and outcome was collected, may indicate that the retrospective registrations biased the self-reported exposure variable.

Another possible explanation for the lack of beneficial impact of physical exercise on risk of VTE is that the specific questionnaires on exercise habits used in the prospective cohorts were inadequate to measure the actual physical activity in the populations. Furthermore, study subjects may wish to report behaviors consistent with a healthy lifestyle, and thus report their exercise habits inaccurately. However, self-reported information on physical exercise was able to show an expected association between physical exercise and lower risk of cardiovascular disease in the same populations.[5,22,23] The latter observations actually imply opposite effects of physical exercise on arterial and venous thrombotic diseases in middle-aged and elderly subjects.

The mechanisms underlying the lack of beneficial effects of physical exercise on risk of VTE are unknown. The favorable association between physical exercise and cardiovascular risk factors, such as blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides and the frequency of diabetes in our study, imply that these cardiovascular risk factors did not significantly modify the risk of venous thrombosis.[5,20,24] Exercise of higher intensity and longer duration is associated with an increased risk of injuries,[25] particularly in elderly,[19] which may lead to an increased risk of VTE through immobilization and a subsequent hypercoagulable state.[19,26,27] Unfortunately, data on minor injuries were not available for our cohort to test this hypothesis. Furthermore, physical exercise of moderate and high intensity is associated with several immediate alterations in the hemostatic system, such as increased platelet reactivity,[28] shortened bleeding-time,[29] elevated plasma levels of factor VIII,[30] von Willebrand factor,[30,31] and fibrinogen,[32] increased plasma viscosity,[32] increased endogenous thrombin formation assessed by thrombin-antithrombin complex formation,[30] and transient increased fibrinolytic activity associated with increased plasma levels of tissue plasminogen activator[33] with subsequent inhibition of fibrinolytic activity monitored by prolongation of whole blood clot lysis time. These acute prothrombotic changes in the hemostatic system may contribute to the increased risk of acute coronary syndromes associated with physical exertion.[34] However, the impact of regular exercise on resting and exercise-induced changes in the hemostatic system is not well known. Standardized interventions with aerobic physical activity for at least 8 weeks have been found to dampen platelet reactivity,[35] increase plasma fibrinogen and factor VIII in the elderly,[36,37] and enhance or not affect fibrinolytic activity,[33,37] whereas endogenous thrombin generation in plasma was decreased or unaltered[33,36] under resting conditions. However, standard training over time enhanced the exercise-induced changes in the coagulation and fibrinolytic systems.[33]

The main strengths of our study are its prospective design, a large number of participants recruited from a general population with high attendance rate, long-term follow-up, and validated VTE events. All hospital care and radiological imaging in the region is provided exclusively by a single hospital, which enhances the possibility of a complete VTE registry. However, the study has some limitations. Modifiable risk factors, such as physical activity, are potential limitations of cohort studies, especially when the time between exposure and disease manifestation is long. This type of non-differential misclassification generally leads to underestimation of true associations. Thus, changes in exercise habits during the study period could have affected our results. However, in the only prospective cohort study which administered repeated questionnaires on exercise habits,[19] similar results were found by statistical analysis of exercise at baseline only and modeled as a time-varying exposure. Further, the exposure variable was not validated against physical fitness status, but the exercise categories in our study were associated with expected[38] beneficial effects on serum lipids, blood pressure, BMI, and frequency of diabetes mellitus.

In conclusion, regular physical exercise of moderate to high intensity in leisure time did not appear to protect against VTE in a general population. High amounts of physical exercise (≥3 h per week) tended to increase the risk of provoked VTE and increase the risk of total VTE in the elderly and obese. However, the overall benefits of regular physical exercise are most likely to be greater than the possible increased risk of venous thrombosis. Further studies are needed to determine the impact of physical activity on the risk of VTE in particular subgroups.

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