

Physical activity and risk of recurrence and mortality after incident venous thromboembolism

Running head: Physical activity and venous thromboembolism

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Essentials:

- Limited data exist on physical activity and risk of complications to venous thromboembolism, VTE
- These associations were explored in VTE patients recruited from the general population
- Physical activity was not association with recurrence risk, but with 28% lower risk of mortality
- This association was most pronounced in patients with incident deep vein thrombosis

Abstract

Background: Limited data exist on the relationship between physical activity and major complications after incident venous thromboembolism (VTE).

Objectives: To investigate whether physical activity was associated with risk of recurrence and mortality in VTE patients recruited from the general population.

Methods: Patients with incident VTE (n=786) derived from the Tromsø Study surveys 4-6 (1994-95, 2001-02 and 2007-08) were included, and data on physical activity was dichotomized according to the activity level reported in the survey preceding the incident VTE (inactive: <1h per week, active: ≥1h per week). Recurrent VTE and all-cause mortality were registered up to December 31, 2015. Hazard ratios (HRs) for recurrence and all-cause mortality were calculated using Cox regression models with the inactive group as reference.

Results: There were 139 recurrences and 395 deaths during follow-up. Physical activity was not associated with the risk of recurrence in men (HR model 2: 1.48, 95% confidence interval (CI) 0.83-2.65) or in women (HR model 2: 0.95, 95% CI 0.52-1.74). In contrast, physical activity was associated with a 28% lower risk of mortality during ten years of follow-up (HR model 3: 0.72, 95% CI 0.57-0.91). The inverse association was stronger in patients with a first deep vein thrombosis (DVT; HR model 2: 0.59, 95% CI 0.44-0.79) than a pulmonary embolism (HR model 3: 0.87, 95% CI 0.61-1.26).

Conclusion: Our results suggest that habitual physical activity prior to incident VTE does not influence the risk of recurrence. In contrast, active individuals were at lower risk of mortality, particularly following a DVT.

Keywords: Epidemiology – Physical activity – Recurrence – Risk factors – Venous thromboembolism

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with adverse consequences at the individual- and population level.

Patients with VTE may suffer from short- and long-term complications, such as thrombus extension and embolization, physical impairment, post-thrombotic syndrome (PTS), recurrent VTE and death [1-4]. Hospital-related VTE is among the leading causes of disability-adjusted life years lost, and it is estimated that more than 500 000 VTE-related deaths occur annually in the European Union [5, 6]. Identification of risk factors for recurrence and mortality may improve risk stratification, secondary prevention, and potentially reduce the overall disease burden of VTE.

Although the risk of recurrence is highest during the first year after the incident event (7-13%), the ten-year cumulative recurrence extends to 30-40% [4, 7, 8]. Characteristics of the incident event, patient demographics and comorbidities largely determine the risk of recurrence. Patients with an incident VTE provoked by a major persistent risk factor (e.g. active cancer) are at the highest risk, those with unprovoked VTE are at intermediate risk, and those with events provoked by a major transient risk factor (e.g. surgery) are at the lowest risk of recurrence [9]. Male sex and excess body weight are also associated with an increased risk of recurrence [10, 11].

Patients with VTE have a higher risk of mortality compared to the general population, especially during the first year after the event [12, 13]. The one-, five, and ten-year cumulative mortality risks are 22-24%, 40-46% and 55%, respectively [4, 13-15]. Increasing age, smoking, confinement to hospital or nursing home, comorbidities and incident PE, are predictors of reduced survival in patients with VTE [13]. Provoked VTE is associated with a higher risk of mortality compared with unprovoked VTE, potentially due to higher age and more comorbidities in patients with provoked events [4, 15]. Cancer-related VTE is associated with the highest risk of mortality [4, 14].

There is robust evidence of an inverse association between physical activity and risk of several adverse health outcomes, including arterial cardiovascular disease (CVD) and premature mortality [16-18]. Several studies, including our recent report, have also suggested a favorable association between physical activity and the risk of incident VTE [19-21]. We found that 1-3 hours per week of light physical activity was associated with a lower VTE risk when compared to <1 hour per week, with limited evidence of additional benefits with increasing amounts of activity [19]. The role of physical activity with regards to VTE related complications is unclear.

To our knowledge, only one study has investigated the association between physical activity and risk of VTE recurrence. The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) follow-up study reported that women with a sedentary lifestyle (prolonged sitting) prior to the incident VTE had a 1.5-fold higher risk of recurrence, while no association was observed in men [22]. However, it is unknown whether regular physical *activity* influences the risk of VTE recurrence. Moreover, despite an inverse association between physical activity and mortality in individuals with established arterial CVD [23, 24], we are only aware of one study investigating this association in patients with VTE [25]. Faller et al. found that elderly VTE patients (≥ 65 years) with a low activity level had an almost two-fold increased risk of mortality during three years of follow-up [25]. However, whether this association applies to VTE patients in general, and in a long-term perspective, remains unclear. Therefore, the aims of the present study were to investigate the association between regular physical activity assessed prior to the incident event and the risk of (i) recurrent VTE and (ii) all-cause mortality in a cohort of VTE patients recruited from a general population.

Methods

Study population

The source population comprised of 30 586 individuals participating in one or more of the Tromsø Study surveys four (1994-95), five (2001-02) and six (2007-08). The Tromsø Study is a single-center population-based cohort study with repeated health surveys of the inhabitants of the Tromsø municipality in Norway. All (Tromsø 4) or parts (Tromsø 5 and 6) of the population were invited to participate, and the attendance rates ranged from 66% to 79%. Detailed methodology of the Tromsø Study is published elsewhere [26]. Individuals who did not consent to medical research (n=181), were not officially registered as inhabitants of the Tromsø municipality at baseline (n=23) and with a pre-baseline history of VTE (n=85), were excluded. The study was approved by the Regional Committee for Medical and Health Research Ethics, and all participants provided written informed consent prior to inclusion.

The process of VTE identification and adjudication in the Tromsø Study has been described in detail previously [27]. Briefly, all incident VTE events from inclusion (1994-95, 2001-02, or 2007-08) to the end of follow-up (December 31, 2015), were identified by searching the hospital discharge registry (outpatient visits and hospitalizations), the autopsy registry and the radiology procedure registry at the University Hospital of North Norway (UNN). UNN is the exclusive provider of all hospital care and relevant diagnostic radiology in the study region. Trained personnel adjudicated and recorded each event by thorough review of the medical records of all potential VTE cases. The adjudication criteria were presence of signs and symptoms of PE or DVT, combined with objective confirmation by radiological procedures, a recorded PE or DVT diagnosis in the patient's journal, and treatment initiation unless contraindications were specified. A total of 858 incident VTE events were recorded during the study period. Of these, 72 were excluded due to missing information on physical activity in the last survey they participated in prior the VTE event, yielding 786 VTE patients eligible for the present study.

Classification of venous thromboembolism

All incident events were classified as either DVT or PE, and concurrent disease was recorded as PE. The events were further classified as unprovoked, provoked or cancer-related. A cancer-related event was recorded if VTE occurred in a patient with overt cancer or if cancer was diagnosed within one year after the VTE event. Cancer-related VTE was recorded regardless of the presence of other provoking factors. In cancer-free individuals, provoked VTE was recorded in presence of recent surgery or trauma (within 8 weeks prior to the event), acute medical conditions (acute myocardial infarction, ischemic stroke, or major infectious disease), marked immobilization (bedrest ≥ 3 days, confined to wheelchair, or long-distance travel ≥ 4 h within the previous 14 days), or another provoking factor described by the physician in the medical record (e.g., intravascular catheters). The remaining VTE events were classified as unprovoked.

Measurements

Participant information was obtained by physical examinations, blood samples and self-administered questionnaires, and data from the most recent survey preceding the incident VTE event was used. Height and weight were measured with participants wearing light clothes with no shoes, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Information on leisure-time physical activity, smoking habits, education, diabetes, and history of CVD (angina pectoris, myocardial infarction and stroke), was collected via self-administered questionnaires.

Assessment and categorization of leisure-time physical activity in the Tromsø Study has been described in detail previously [19]. Briefly, participants in Tromsø 4 and 5 reported their average weekly time spent in light (not sweating or out of breath) and hard physical activity (causing sweating and breathlessness) during the past year according to four categories (none, <1 hour, 1-2 hours or ≥ 3 hours). Participants in Tromsø 6 reported their weekly frequency of exercise (never, less than once,

once, 2-3 times or approximately every day), intensity (not short-winded or sweaty, becoming short-winded or sweaty or becoming exhausted), and average duration per session (<15 minutes, 15-29 minutes, 30-60 minutes or >1 hour). Total weekly duration of physical activity was calculated as the sum of frequency and duration, and categories similar to those in Tromsø 4 and 5 were created. The two upper intensity-categories were considered equivalent to hard physical activity in Tromsø 4 and 5, and the lowest intensity category equivalent to light physical activity. A common dichotomous activity variable was created, where the active group comprised of participants reporting physical activity ≥ 1 hour per week and the inactive group of those reporting no physical activity or <1 hour per week, regardless of intensity. We also constructed a five-level variable where the inactive group was kept unchanged and the active groups were divided in four: '1–3 hours per week of light activity', '>3 hours per week of light activity', '1–3 hours per week of hard activity', and '>3 hours per week of hard activity'.

Outcome registration

All recurrent VTE events and deaths were recorded throughout the study period (i.e. from date of incident VTE up to December 31, 2015). Recurrent VTEs were identified and adjudicated using the same criteria as the incident events described above. Information on mortality was obtained from the Norwegian Population Registry.

Statistical analyses

For analyses of recurrence, person-years of follow-up were accrued from the date of the incident VTE to the date of recurrence, death, migration or to the end of the study period (December 31, 2015), whichever came first. The analytical setup was identical for the mortality analyses, except that recurrent VTE and migration were not included as censoring events. In cases where incident VTE and

death occurred on the same date (n=18), one day of follow-up was recorded for the mortality analyses.

All statistical analyses were performed with STATA version 15.1 (Stata Corp, College Station, TX, USA). The one-, five- and ten-year cumulative risks of recurrence and mortality according to physical activity status were estimated and illustrated with the Kaplan-Meier (KM) failure function (1-KM) and the KM survivor function, respectively. The crude recurrence and mortality rates with 95% confidence interval (CIs) according to physical activity status were calculated and expressed as number of recurrences or deaths per 100 person-years. Hazard ratios (HRs) with 95% CIs were estimated in Cox proportional hazards regression models with the inactive group as the reference. The analyses were also performed across five levels of weekly physical activity to explore a potential dose-dependent relationship. Time on study was used as time scale in the recurrence analyses, and age was used as time scale in the mortality analyses. The choice of time scale (i.e. attained age or time on study) was based on the strength of the association between time scale and the outcome (e.g. the risk of recurrent VTE was regarded to be more strongly dependent on time on study than on age) [28]. The analyses were performed in two models for recurrence and in three models for mortality. For recurrence, model 1 included age and sex, while model 2 included model 1 + BMI, history of CVD and cancer-related VTE. Due the higher recurrence risk among men, sex-stratified analyses were also performed for the association between physical activity and risk of recurrence [11]. For mortality, model 1 include age (as time scale) and sex, model 2 included model 1 + BMI, education and current smoking, while model 3 included model 2 + history of CVD and cancer-related VTE. IRs and HRs according to physical activity status were estimated for overall recurrence and mortality with one, five and ten years of follow-up, and in subgroups stratified by characteristics of the incident events with ten years of follow-up. Due to high mortality in patients with cancer-related VTE, the stratified analyses were restricted to five years of follow-up for recurrence and mortality in this group. There were 5 participants with missing information on BMI and 12 with missing information on education, and these were omitted from multivariable analyses only.

The risk of recurrence may be overestimated when the mortality risk is high and differs between exposure groups [29, 30]. In order to take competing risk by death into account, cumulative incidence functions and subdistribution hazard ratios (SHR) were estimated according to the method of Fine and Gray [29].

The proportional hazards assumption was evaluated and verified on basis of Schoenfeld residuals and by visual inspection of the curves of the log-log survival function. Statistical interactions between physical activity and sex (physical activity*sex) and physical activity and age (physical activity*age) were tested by including the cross-product terms separately in the fully adjusted regression model, and no interactions were found. As the interaction between physical activity and age is tested through the proportional hazards assumption tests when age is used as time scale, this interaction-term was not relevant in the analyses of mortality.

The analyses were conducted under the assumption that physical activity habits prior to the incident VTE event are representative for the level of activity after the event. For a subgroup of individuals with data on physical activity in a Tromsø survey after the incident VTE (n=131), we describe the proportions with the same, higher and lower activity level overall, and separately for patients with PE and DVT.

Results

The median time between data collection at the most recent survey and the incident VTE event was 5.5 years (interquartile range: 3.0-9.6 years). The mean age at incident VTE was 68 (± 14) years, and 51% were women. In total, 38.3% of the events were unprovoked, 34.1% provoked (non-cancer) and 27.6% were cancer-related. Participant characteristics obtained in the Tromsø survey preceding the incident VTE and clinical characteristics at the time of the incident VTE according to activity status are shown in Table 1. Physically active participants were slightly younger at the time of the incident VTE, were less frequently women and less likely to have a history of CVD. The proportion of non-cancer

provoked events were similar between active and inactive, while there was a larger proportion of unprovoked VTE among the active and a larger proportion of cancer-related VTE among the inactive. The planned duration of anticoagulant treatment was essentially similar in active and inactive patients, although the proportion receiving >6 months of treatment appeared somewhat larger among the inactive. The distribution of provoking factors and clinical risk factors also differed according to activity status. The prevalence of immobilization, obesity and medical conditions (acute and other) was higher among the inactive, while family history of VTE was more frequent among the active.

In the subgroup of patients with data on physical activity in a Tromsø survey *after* the incident VTE event (n=131), the mean age at the incident event was 62 (\pm 9) years, 41% were women, and 64% had a DVT as the first event. Of these, 75% remained in the same activity category as before the VTE, 18% went from active to inactive, and 7% went from inactive to active. The corresponding numbers were 70%, 19% and 11% in patients with PE, and 77%, 18% and 5% in patients with DVT.

Recurrence

During a median follow-up of 2.9 years, there were 139 VTE recurrences and the overall recurrence rate was 3.7 per 100 person-years. The cumulative recurrence risk was higher in the physically active individuals throughout follow-up (Fig. 1). At one year, the cumulative recurrence was 5.3% (95% CI 2.9-9.3) in the inactive and 7.7% (95% CI 5.6-10.5) in the active. The corresponding numbers were 15.7% (95% CI 10.8-22.7) and 19.3% (95% CI 15.6-23.7) at five years, and 25.2% (95% CI 17.0-36.3) and 31.3 (95% CI 25.9-37.5) at ten years. When expressed in the Cox regression model, there were no significant associations between physical activity and the risk of recurrent VTE (Table 2, Table S1). However, the risk estimates suggested a higher recurrence risk among active compared to inactive individuals, particularly at one year of follow-up (Table 2, HR Model 2: 1.53, 95% CI 0.77-3.05). The

risk estimates were unchanged when adjusting for planned duration of anticoagulant treatment (data not shown).

Sex-stratified analyses are shown in Table 3. Again, there were no significant associations between physical activity and recurrence risk in either men or women. However, the risk estimates were suggestive of a higher recurrence risk in active men after both five years (HR model 2: 1.27, 95% CI 0.68-2.35) and ten years (HR model 2: 1.48, 95% CI 0.83-2.65). Similarly, when analyses were conducted across five levels of physical activity for ten-year recurrence risk, a higher weekly amount was associated with a progressively higher recurrence risk in men (Table S1). However, most of the point estimates did not reach statistical significance, and these results must be interpreted with caution. In women, the corresponding five- and ten-year risk estimates were close to one, but in opposite directions. Notably, there were very few recurrences (n=7) between five and ten years of follow-up in women. The power of the dose-response analyses in women were limited by few events in the higher activity categories, but were suggestive of a lower ten-year recurrence risk with high weekly activity (Table S1).

Analyses of the ten-year recurrence risk according to activity status stratified by characteristics of the incident event are shown in Table 4. Although, there were no significant associations between physical activity and recurrence risk, the risk estimates were suggestive of a higher recurrence risk in active compared to inactive individuals after provoked VTE (HR model 2: 1.66, 95% CI 0.72-3.81) and PE (HR model 2: 1.35, 95% CI 0.64-2.82).

Mortality

There were 395 deaths during a median follow-up of 4.1 years, and the overall mortality rate was 8.8 per 100 person-years. As shown in Fig. 2, the ten-year survival probability was lower in inactive compared to active individuals. The cumulative mortality at one year was 26.5% (95% CI 21.5-32.4) in the inactive and 20.8% (95% CI 17.6-24.5) in the active, and the mortality remained higher among the

inactive at both five years (48.5%, 95% CI 42.1-55.3 versus 35.7%, 95% CI 31.6-40.0) and ten years of follow-up (65.2%, 95% CI 57.9-72.4 versus 49.0%, 95% CI 44.4-53.9). The adjusted one-, five- and ten-year mortality risk according to physical activity status are shown in Table 5. There was a non-significant trend of a lower one-year mortality risk among active individuals (HR model 3: 0.81, 95% CI 0.57-1.17). At five and ten years of follow-up, the fully adjusted mortality risk was significantly 25% and 28% lower, respectively, in active compared to inactive individuals. In analyses of the ten-year mortality risk across five categories of physical activity, there was a threshold effect where light physical activity ≥ 1 hour per week (>the reference category) was associated with a lower risk compared to <1 hour per week, with no additional benefit with increasing amounts of physical activity (Table S2).

Table 6 shows the ten-year mortality risk by physical activity status stratified by characteristics of the incident event. Physical activity was associated with a lower risk of mortality after provoked (HR model 2: 0.63, 95% CI 0.40-0.97) and unprovoked VTE (HR model 2: 0.63, 95% CI 0.40-0.99), while no association was observed for cancer-related VTE (five-year mortality risk reported due to high mortality rates). The ten-year cumulative mortality rates and risks according to physical activity status for PE and DVT are shown in Fig. 3A/Fig. 3B and Table 6. While no significant association was observed in patients with PE (HR model 2: 0.87, 95% CI 0.61-1.26), the ten-year mortality risk following DVT was 41% lower among active compared to inactive individuals (HR model 2: 0.59, 95% CI 0.44-0.79).

Competing risk by death

The cumulative incidence of recurrence dropped when competing risk by death was taken into account. At one, five and ten years, the cumulative incidences were 4.6%, 10.8% and 15.8% among the inactive, and 6.2%, 14.4% and 20.9% among the active, respectively. Overall, the point estimates

for the SHR were somewhat higher than the HRs estimated from the Cox regression (Tables 2-4 and Table S1).

Discussion

In the present study, we investigated the association between habitual physical activity and the risk of recurrence and mortality in patients with incident VTE recruited from a general population. Our main findings were that (i) physical activity was associated with a lower risk of mortality, (ii) the inverse association appeared mainly in patients with DVT as the incident event, and (iii) there was no association between physical activity and the risk of VTE recurrence.

Despite an excess mortality risk in patients with VTE and convincing evidence of an inverse association between physical activity and the risk of premature mortality, this relationship has so far received little attention. One study conducted in elderly VTE patients reported that a low level of physical activity was associated with an almost two-fold higher risk of mortality during three years of follow-up [25]. We extend these findings showing that physical activity (≥ 1 hour per week) was associated with 19-28% lower mortality risk compared to being inactive (< 1 hour per week) across one to ten years of follow-up in VTE patients with a wide age-range recruited from a general population. An inverse association between physical activity and mortality has previously been reported in general populations, across age groups and in relation to diseases such as cancer and arterial CVD, with a reported magnitude of risk reduction in the range 10-40% [16, 17, 24].

The beneficial association between physical activity and mortality mainly appeared in patients with DVT as the incident event, while no clear association was observed in relation to PE. Compared to isolated DVT, PE is generally associated with a higher short-term (< 1 year) mortality, although the difference decreases over time and the longer-term (> 1 year) cumulative mortality risks are comparable [12, 14, 31]. The most frequently reported causes of death in patients with VTE are cancer, PE, other cardiovascular or respiratory diseases, and infections [14, 25, 31]. Previous studies

have shown that the site of the incident VTE is predictive of the site of a potential recurrence, i.e. a PE most often recur as a new PE and vice versa [4, 32]. Further, although the incidence of cancer is reported to be similar in DVT and PE [33, 34], patients with PE appear to be at a higher risk of myocardial infarction [35]. Potentially, such PE-specific complications may partly overwhelm a protective effect of physical activity on mortality, and explain the weaker association between physical activity and survival observed in patients with PE compared to DVT in the present study.

In contrast to our findings, Faller et al. reported that the inverse association between physical activity and mortality was largely driven by an effect in patients with PE (\pm DVT) [25]. There are several plausible explanations for the apparently diverging findings. Faller et al. assessed physical activity habits at the time of the incident VTE, while we used data obtained prior to the event. Assessing physical activity at the time of acute disease may introduce information bias, particularly in patients with PE, which is the more severe form of VTE. Further, their definition of PE was less stringent than in the present study, in that a confirmed proximal DVT together with clinical symptoms of PE was classified as PE without additional radiological procedures. The prevalence of PE was high (69%) compared to the present (42%) and other population-based studies [14, 36]. Finally, although we did not observe any interaction between physical activity and age in the present study, the age difference between the study populations (75 years vs. 68 years) may have influenced the findings.

Few studies have investigated the association between physical activity and the risk of VTE recurrence. Our findings indicate that habitual physical activity is not related to recurrence risk, as shown in both traditional Cox regression and in competing risk by death analyses. As expected, the SHRs were somewhat higher than the HRs, which is explained by the difference in mortality between active and inactive individuals. Apparently conflicting, in the MEGA follow-up study, Flinterman et al. found that a sedentary lifestyle (prolonged sitting) assessed at the time of incident VTE was associated with an increased risk of recurrence in women, while no association was observed in men

[22]. As it is possible for an individual to accumulate a large amount of both active and sedentary time (e.g. sitting hours) during a day, it has been suggested that physical activity and sedentary behavior should be considered as separate risk factors [37]. Accordingly, the two studies are not directly comparable.

We and others, have previously reported a beneficial association between habitual physical activity and the risk of incident VTE [19-21]. In recurrence research, the phenomenon “recurrence paradox” is often encountered, referring to the situation where a risk factor is differently related to first and recurrent events [38]. Because the risk of incident and recurrent VTE are compared on different scales (i.e. in the general population and in the VTE population), the impact of a risk factor (e.g. physical activity) will appear different [38]. In addition, the paradox may also occur due to index event bias, which arises when patients are selected based on the occurrence of an index event (e.g. incident VTE), and may result in underestimated or even reversed associations [39]. Accordingly, the lack of an association between physical activity and VTE recurrence, which contrasts previous findings in relation to incident VTE, may be due to aspects inherent in the research methodology.

In the present study, habitual physical activity was assessed prior to the incident event. In the subgroup of patients who returned to a survey after their incident event, 75% remained at the same activity level, while 25% changed behavior. A recent study in women with incident VTE reported that a VTE event was associated with a clinically significant decline in physical function equivalent to more than five years of aging, which was particularly pronounced in those with PE [3]. There are several consequences of VTE that may influence the post-event activity level, such as PTS, chronic pulmonary thromboembolic pulmonary hypertension, impaired physical function and capacity, as well as fear of complications in relation to exercise [2, 3, 40, 41]. Although, physical activity was associated with an expected lower risk of mortality in our study, non-differential misclassification of the exposure may be present leading to an underestimation of the true associations [42].

The main strengths of the present study include VTE patients recruited from a general population, wide age distribution, prospective design, and thoroughly validated and adjudicated outcomes. As UNN is the only provider of hospital care in the study region, a near complete VTE register can be anticipated. To our knowledge, this is the first study to investigate the association between habitual physical activity and the risk of VTE recurrence, and among the first to address the influence of physical activity on the risk of mortality in patients with VTE. There are some limitations that merit consideration. The analyses were restricted to participants who had provided information on their physical activity habits (92%), and the responders may differ from the non-responders. Further, as physical activity was assessed via self-report, there is a chance for misclassification (e.g., due to challenges with recall or social desirability). Likewise, changes in activity behavior following the incident event, may have induced misclassification. However, this is likely to be independent of the outcome and not a threat to the internal validity of the study. A methodological challenge in our study was the use of different questionnaires to assess physical activity in the different surveys of the Tromsø Study. However, the activity categories are shown to be meaningfully associated with cardiometabolic markers, which supports the validity of the variable [19].

In conclusion, habitual physical activity was associated with lower risk of mortality in patients with VTE, and DVT in particular. In contrast, the risk of VTE recurrence appeared not to be influenced by physical activity.

Addendum

L.H. Evensen analyzed the data and drafted the manuscript. T. Isaksen collected data and revised the manuscript. S. K. Brækkan and J.-B. Hansen were responsible for conception and design of the study, data collection, and revision of the manuscript. The manuscript has been read and approved for submission to the Journal of Thrombosis and Haemostasis by all authors.

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Tables and figures

Table 1 Baseline and clinical characteristics of patients with incident VTE (n=786)

	Inactive (n=251)	Active (n=535)
Baseline characteristics		
Age at incident VTE (years), mean (\pm SD)	70 (\pm 14)	66 (\pm 13)
Sex (women), % (n)	58.2 (146)	47.7 (255)
Body mass index (kg/m ²), mean (\pm SD)*	27.8 (\pm 5.1)	27.1 (\pm 4.4)
Education, % (n)*	18.0 (44)	23.8 (126)
Current smoking, % (n)*	29.1 (73)	28.6 (153)
History of cardiovascular disease, % (n) [†]	19.9 (50)	15.1 (81)
Clinical presentation, % (n)		
Deep vein thrombosis	56.2 (141)	58.3 (312)
Pulmonary embolism	43.8 (110)	41.7 (223)
Unprovoked	36.7 (92)	39.1 (209)
Cancer-related [‡]	29.9 (75)	26.5 (142)
Provoked [§]	33.5 (84)	34.4 (184)
Planned treatment duration with AC, % (n)		
0-3 months	36.7 (92)	35.5 (190)
3-6 months	31.5 (79)	36.5 (195)
6-12 months	21.5 (54)	18.5 (99)
> 12 months	10.4 (26)	9.5 (51)
Provoking factors, % (n)		
Surgery	16.4 (41)	16.5 (88)
Trauma	10.0 (25)	9.4 (50)
Acute medical condition	14.8 (37)	12.3 (66)
Immobilization [¶]	20.7 (52)	16.5 (88)
Other provoking factor ^{**}	6.0 (15)	4.1 (22)
Clinical risk factors, % (n)		
Obesity ^{††}	22.2 (54)	16.3 (84)
Family history ^{‡‡}	2.0 (5)	3.9 (21)
Other medical conditions ^{§§}	30.7 (67)	16.9 (79)
Pregnancy/postpartum (of cases in women)	0.68 (1)	1.96 (5)
Estrogen use (of cases in women) ^{¶¶}	9.7 (14)	10.6 (27)

*Assessed at the most recent survey prior to the incident VTE event, †Angina pectoris, stroke or myocardial infarction, ‡Active cancer or cancer diagnosed within one year after the VTE event, §Excluding cancer, ¶Bed rest ≥3 days, long-distance travel ≥4 h within the previous 14 days, or confined to wheelchair, **Other factors specified as provoking in the medical record (e.g., intravascular catheters), ††Body mass index ≥30 kg/m² at the time of incident VTE, ‡‡ Reported family history of VTE in first-degree relative(s) before the age of 60, §§Other diseases within the previous year (myocardial infarction, ischemic stroke heart failure, inflammatory bowel disease, or myeloproliferative disorders), ¶¶Hormone replacement therapy or oral contraceptives.

AC anticoagulants, SD standard deviation, VTE venous thromboembolism.

Values are mean (SD) or percentage (count).

Table 2 Incidence rates and hazard ratios with 95% confidence intervals for one-, five- and ten-year venous thromboembolism recurrence by physical activity status. The Tromsø Study 1994-2015.

	Person-years	Events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR model 2 (95% CI)‡	SHR (95% CI)‡
One-year recurrence						
Inactive	189	11	5.83 (3.23-10.53)	1	1	1
Active	431	35	8.13 (5.84-11.32)	1.52 (0.77-3.02)	1.53 (0.77-3.05)	1.65 (0.85-3.21)
Five-year recurrence						
Inactive	647	26	4.02 (2.73-5.90)	1	1	1
Active	1571	75	4.78 (3.81-5.99)	1.26 (0.80-1.97)	1.23 (0.78-1.93)	1.32 (0.84-2.08)
Ten-year recurrence						
Inactive	882	31	3.51 (2.47-5.00)	1	1	1
Active	2354	98	4.16 (3.42-5.07)	1.23 (0.81-1.85)	1.22 (0.81-1.84)	1.36 (0.91-2.04)

*Per 100 person-years, †Adjusted for age and sex, ‡Model 1+ body mass index, history of cardiovascular disease and cancer-related VTE.

CI confidence interval, HR hazard ratio, IR incidence rate, SHR subdistribution hazard ratio, VTE venous thromboembolism.

Table 3 Incidence rates and hazard ratios with 95% confidence intervals for five- and ten-year venous thromboembolism recurrence by physical activity status stratified by sex. The Tromsø Study 1994-2015.

	Person-years	Events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR model 2 (95% CI)‡	SHR (95% CI)‡
Five-year recurrence						
Men						
Inactive	265	13	4.91 (2.85-8.45)	1	1	1
Active	819	47	5.74 (4.31-7.64)	1.31 (0.71-2.44)	1.27 (0.68-2.35)	1.40 (0.76-2.57)
Women						
Inactive	382	13	3.40 (1.97-5.85)	1	1	1
Active	752	28	3.73 (2.57-5.40)	1.16 (0.60-2.26)	1.16 (0.59-2.28)	1.24 (0.62-2.48)
Ten-year recurrence						
Men						
Inactive	343	14	4.08 (2.42-6.89)	1	1	1
Active	1219	67	5.50 (4.33-6.98)	1.47 (0.82-2.63)	1.48 (0.83-2.65)	1.69 (0.96-2.99)
Women						
Inactive	539	17	3.15 (1.96-5.07)	1	1	1
Active	1135	31	2.73 (1.92-3.88)	0.96 (0.53-1.74)	0.95 (0.52-1.74)	1.03 (0.56-1.90)

*Per 100 person-years, †Adjusted for age, ‡Model 1+ body mass index, history of cardiovascular disease and cancer-related VTE.

CI confidence interval, HR hazard ratio, IR incidence rate, SHR subdistribution hazard ratio, VTE venous thromboembolism.

Table 4 Incidence rates and hazard ratios with 95% confidence intervals for ten-year venous thromboembolism recurrence by physical activity status stratified by characteristics of the incident event. The Tromsø Study 1994-2015.

	Person-years	Events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR model 2 (95% CI)‡	SHR (95% CI)‡
Unprovoked						
Inactive	434	14	3.23 (1.91-5.45)	1	1	1
Active	1144	40	3.50 (2.56-4.77)	1.10 (0.60-2.04)	1.08 (0.58-2.02)	1.18 (0.62-2.23)
Provoked						
Inactive	329	7	2.13 (1.01-4.46)	1	1	1
Active	966	34	3.52 (2.52-4.93)	1.65 (0.72-3.77)	1.66 (0.72-3.81)	2.04 (0.91-4.54)
Cancer-related§						
Inactive	97	10	10.27 (5.53-19.09)	1	1	1
Active	190	21	11.06 (7.21-16.96)	1.02 (0.48-2.16)	0.99 (0.45-2.15)	1.01 (0.48-2.13)
Deep vein thrombosis						
Inactive	477	21	4.40 (2.87-6.74)	1	1	1
Active	1426	67	4.70 (3.70-5.97)	1.14 (0.69-1.87)	1.09 (0.66-1.80)	1.31 (0.80-2.15)
Pulmonary embolism						
Inactive	405	10	2.47 (1.33-4.59)	1	1	1
Active	928	31	3.34 (2.35-4.75)	1.30 (0.63-2.67)	1.35 (0.64-2.82)	1.40 (0.68-2.88)

*Per 100 person-years, †Adjusted for age and sex, ‡Model 1+ body mass index, §Follow-up restricted to 5 years. CI confidence interval, HR hazard ratio, IR incidence rate, SHR subdistribution hazard ratio, VTE venous thromboembolism.

Table 5 Mortality rates and hazard ratios with 95% confidence intervals for one-, five- and ten-year mortality in patients with incident venous thromboembolism by physical activity status. The Tromsø Study 1994-2015.

	Person-years	Deaths	Crude MR (95% CI)*	HR model 1 (95% CI)†	HR model 2 (95% CI)‡	HR model 3 (95% CI)§
One-year mortality						
Inactive	193	66	34.16 (26.84-43.48)	1	1	1
Active	444	110	24.77 (20.55-29.86)	0.87 (0.62-1.20)	0.87 (0.62-1.21)	0.81 (0.57-1.17)
Five-year mortality						
Inactive	695	113	16.26 (13.53-19.56)	1	1	1
Active	1755	181	10.31 (0.91-11.93)	0.73 (0.57-0.93)	0.71 (0.55-0.91)	0.75 (0.57-0.97)
Ten-year mortality						
Inactive	983	136	13.83 (11.69-16.37)	1	1	1
Active	2778	229	8.24 (7.24-9.38)	0.68 (0.55-0.85)	0.67 (0.53-0.83)	0.72 (0.57-0.91)

*Per 100 person-years, †Adjusted for age (as time scale) and sex, ‡Model 1 + body mass index, current smoking and education, §Model 2 + history of cardiovascular disease and cancer-related VTE.

CI confidence interval, HR hazard ratio, MR mortality rate, VTE venous thromboembolism.

Table 6 Mortality rates and hazard ratios with 95 % confidence intervals for ten-year mortality in patients with incident venous thromboembolism by physical activity status stratified by characteristics of the incident event. The Tromsø Study 1994-2015.

	Person-years	Deaths	Crude MR (95% CI)*	HR model 1 (95% CI)†	HR model 2 (95% CI)‡
Unprovoked					
Inactive	490	39	7.95 (5.81-10.88)	1	1
Active	1401	57	4.07 (3.14-5.27)	0.70 (0.46-1.07)	0.63 (0.40-0.99)
Provoked					
Inactive	354	39	11.02 (8.05-15.08)	1	1
Active	1101	56	5.09 (3.91-6.61)	0.58 (0.38-0.90)	0.63 (0.40-0.97)
Cancer-related§					
Inactive	113	54	47.75 (36.58-62.35)	1	1
Active	207	113	54.66 (45.46-65.73)	1.01 (0.71-1.44)	1.10 (0.74-1.62)
Deep vein thrombosis					
Inactive	536	88	16.39 (13.30-20.20)	1	1
Active	1705	129	7.56 (6.37-8.99)	0.56 (0.43-0.74)	0.59 (0.44-0.79)
Pulmonary embolism					
Inactive	446	48	10.76 (8.11-14.27)	1	1
Active	1073	100	9.32 (7.66-11.34)	0.95 (0.67-1.37)	0.87 (0.61-1.26)

*Per 100 person-years, †Adjusted for age (as time scale) and sex, ‡Model 1 + body mass index, education and current smoking. §Follow-up restricted to 5 years.

CI confidence interval, HR hazard ratio MR mortality rate, VTE venous thromboembolism.

Fig. 1 Cumulative incidence of venous thromboembolism (VTE) recurrence according to physical activity status (inactive: <1h per week, active: \geq 1h per week). The Tromsø Study 1994-2015.

Fig. 2 Survival probability after venous thromboembolism (VTE) according to physical activity status (inactive: <1h per week, active: \geq 1h per week). The Tromsø Study 1994-2015.

Fig. 3 Survival probability after venous thromboembolism (VTE) in patients with incident deep vein thrombosis (Panel A) and pulmonary embolism (Panel B) according to physical activity status (inactive: <1h per week, active: \geq 1h per week). The Tromsø Study 1994-2015.