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Repeated assessments of physical activity and risk of incident venous thromboembolism

Running head: Physical activity and venous thromboembolism

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Essentials:

- It is debated whether physical activity influences the risk of venous thromboembolism.
- The association was explored to account for fluctuations in physical activity over time.
- Overall and in the elderly, physical activity (≥1h/week) was associated with 23% and 30% lower risk.
- A moderate proportion of the association (14-36%) was mediated via body mass index.

Abstract

Background: Whether physical activity influences the risk of incident venous thromboembolism (VTE) remains controversial, potentially due to methodological challenges, such as regression dilution bias.

Objectives: To investigate whether physical activity was associated with VTE risk, and explore the role of body mass index (BMI) as a mediator in a population-based cohort with repeated assessments of physical activity.

Methods: Participants (n=30 002) attending one or more surveys of the Tromsø Study 4-6 (1994-95, 2001-02, 2007-08) were included and categorized based on weekly physical activity. Incident VTE was registered until December 31, 2016. Hazard ratios (HRs) were calculated using time-varying Cox regression models. The Aalen additive hazard model was used to quantify the total, direct and indirect effect of physical activity.

Results: There were 531 incident VTEs during follow-up. Physical activity (≥1/week) was associated with lower risk of VTE (HR 0.77, 95% CI 0.64-0.92) compared to inactive. The effect was most pronounced for those ≥65 years (HR 0.70, 95% CI 0.55-0.88) and provoked events (HR 0.66, 95% CI 0.50-0.89). The difference in absolute risk between active and inactive was -0.42 (95% CI -0.73 to -

0.14) and -1.59 (95% CI -2.74 to -0.52) events annually per 1 000 individuals in the total and elderly population, respectively. A moderate proportion of the association (14-36%) was mediated via BMI.

Conclusion: Our findings suggest that regular physical activity is associated with lower risk of VTE, particularly in elderly. The association occurred at a low weekly amount of physical activity, and was only partly mediated by BMI.

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

Introduction

Venous thromboembolism (VTE) affects 1-2 per 1000 individuals annually, and represents a significant public health burden due to debilitating complications, high recurrence rates and a potentially fatal outcome [1-4]. The individual susceptibility to VTE depends on complex interactions between inherited, acquired and environmental factors with accompanying changes in the vessel wall, blood flow or blood composition of sufficient magnitude to exceed the thrombosis threshold [5, 6]. Despite increased awareness and preventive measures, the age-adjusted incidence rate of VTE has remained stable or increased slightly during the past decades [2, 7]. Moreover, with a growing prevalence of important risk factors, such as cancer, obesity and an aging population, the total number VTE events may rise further in the coming years [8-10]. Hence, identification of modifiable risk factors at the population level is imperative to combat the growing burden of VTE.

Inadequate physical activity is a well-known risk factor for arterial thrombotic diseases [11, 12]. However, despite a bidirectional relationship between arterial and venous thromboembolic diseases [13-15], the association between physical activity and VTE risk remains unsettled. Several studies have suggested that a moderate amount of weekly physical activity is associated with lower risk of incident VTE when compared to no or a low amount of physical activity [16-20]. Specifically, a 4-41% lowered risk of VTE was reported in the ARIC Study [16], the Million Women Study [18] and

the REGARDS Study [17]. However, except for the REGARDS Study, there is limited evidence of a dose-response relationship between physical activity and VTE risk [16-18]. On the contrary, it has been suggested that strenuous activity may be associated with an increased risk of VTE [18, 21], particularly in the elderly [22]. Still, findings from several large cohort studies suggest that physical activity does not influence the risk of VTE in either direction [23-27].

Despite an apparently complex picture, some trends may be deduced from the available literature. First, studies reporting no association between physical activity and VTE risk are characterized by a relatively long follow-up [23-26]. Due to the potential fluctuating nature of physical activity, the risk estimates in these studies may be underestimated due to regression dilution [28, 29]. To date, we are aware of only two studies, restricted to middle-aged [16] and elderly [22], which have accounted for changes in activity habits during follow-up. Further, studies with a retrospective assessment strategy have consistently reported a beneficial association [19, 20]. However, these findings may be subject to recall bias, and should be interpreted with caution [30]. In most studies, body mass index (BMI) has been treated as a confounder of the association between physical activity and VTE [16, 18, 23, 24]. However, as physical activity is important in weight maintenance [12, 31], BMI may be considered as an intermediate, rather than a confounder, in the pathway between physical activity and VTE risk. Therefore, the aims of the present study were (i) to investigate the association between habitual physical activity and the risk of incident VTE in a population-based cohort with repeated assessments of physical activity and observation periods of short duration, and (ii) to explore the role of BMI as a mediator of the association.

Methods

Study population

A total of 30 586 participants were recruited from the fourth (1994-95), fifth (2001-02) and sixth (2007-08) surveys of the Tromsø Study, a prospective population-based study with repeated health surveys of the inhabitants of Tromsø, Norway. Detailed methodology and demographics of the

Tromsø Study have been described previously [32]. Briefly, the participation rates were 77% in Tromsø 4, 79% in Tromsø 5 and 66% in Tromsø 6, and the participants were aged 25 to 89 years at inclusion. Individuals who did not consent to medical research (n=181), were not officially registered as inhabitants of the Tromsø municipality at baseline (n=23), with a pre-baseline history of VTE (n=85), and with missing data on physical activity (n=295), were excluded. Accordingly, 30 002 individuals were included in the present study. Those attending two (n=8541) or three (n=3397) surveys had their exposure data updated and contributed with observation periods corresponding to the number of surveys they participated in, yielding a total of 45 337 observation periods. The study was approved by the Regional Committee for Medical and Health Research Ethics, and all participants signed an informed consent form prior to inclusion.

Measurements

Information at baseline and subsequent visits was obtained by physical examinations, blood samples and self-administered questionnaires. Height and weight were measured with participants wearing light clothes and no shoes, and 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 cardiovascular disease (CVD; angina pectoris, myocardial infarction and stroke), was collected via self-administered questionnaires. Data on cancer history was obtained from the Cancer Registry of Norway.

Assessment and categorization of leisure time physical activity

In Tromsø 4 and 5, participants reported their average weekly time spent in light physical activity (not sweating or out of breath) and hard physical activity (causing sweating and breathlessness) during leisure time in the past year according to four categories: 'none', '<1 hour', '1-2 hours', or '≥3 hours'. The reliability of the question on hard physical activity has been shown to be moderate, and it is reasonably well correlated with data from motions sensors, maximal oxygen uptake (VO_{2max}) and

the International Physical Activity Questionnaire (IPAQ) [33]. The question on light physical activity is reported to be less reliable and less well correlated with objective measures [33]. In Tromsø 6, the participants 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'). The reliability of the questionnaire is reported to be high, and it is well correlated with objective measures of physical activity, IPAQ and VO_{2max} [34]. Total weekly duration of physical activity was calculated as the sum of the reported frequency per week and duration per session, and activity categories equal to those in Tromsø 4 and 5 were created. The lowest intensity-category was considered as equivalent to light physical activity in Tromsø 4 and 5, and the two upper intensity-categories were assumed to reflect hard physical activity. Those who did not report on the intensity question, but provided information on frequency and duration, were placed in the lowest intensity category.

We further constructed a common five-level variable with one inactive group that comprised of participants reporting 'no activity' or 'less than 1 hour per week', and four active groups: '1-3 hours/week of light activity', '>3 hours/week of light activity', 1-3 hours/week of hard activity' and '>3 hours/week of hard activity'. The categorization was based on a combination of the light and hard physical activity questions (Table S1), and was an attempt to apprehend the larger physiological responses with increasing intensity and amount of physical activity [35]. We also created a dichotomous activity variable, where the four active groups were merged (i.e., '≥1 hour/week') and compared to the inactive group (i.e., 'no activity' or '<1 hour/week').

Identification and adjudication of venous thromboembolism

All incident VTE events were identified by searching the hospital discharge registry (both outpatient visits and hospitalizations), the autopsy registry and the radiology procedure registry at the University Hospital of North Norway (UNN) from the date of enrollment (1994-95, 2001-02, or 2007-

08) to December 31, 2016. UNN is the only hospital in the study region, and all hospital care and relevant diagnostic radiology is provided exclusively by this hospital. Trained personnel adjudicated and recorded each VTE event by extensive review of the medical records. The adjudication criteria for VTE were presence of signs and symptoms of pulmonary embolism (PE) or deep vein thrombosis (DVT) combined with objective confirmation by radiological procedures, which resulted in treatment initiation (unless contraindications were specified). The process of case identification and adjudication has previously been described in detail [36].

All VTE events were classified as either DVT or PE (with or without DVT), and as unprovoked or provoked. The following factors were regarded as provoking: recent surgery or trauma (within 8 weeks prior to the event), acute medical conditions (acute myocardial infarction, ischemic stroke, or major infectious disease), active cancer, 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).

Statistical analysis

For each participant, person-years of follow-up were accrued from the date of enrolment to the date of incident VTE, death, migration or to the end of the observation period, whichever came first. Each observation period ended on the date of the next possible survey for participants enrolled in Tromsø 4 (1994/95-2002) or Tromsø 5 (2001/02-2008), while follow-up for Tromsø 6 (2007/08) ended on December 31, 2016. Participants attending only Tromsø 4 and 6 did not contribute with person-years between Tromsø 5 and 6 (Fig. 1). Participants who experienced a VTE event in one observation period, were excluded from subsequent periods. During follow-up, 4940 participants moved from the Tromsø municipality and 4975 participants died.

Crude incidence rates (IRs) for VTE were calculated across categories of physical activity and expressed as number of events per 1000 person-years. Hazard ratios (HRs) with 95% confidence intervals (CIs) for total, unprovoked and provoked VTE, as well as PE and DVT, were estimated using

time-varying Cox proportional hazards regression models with the least active group ('no activity' or '>1 hour/week') as the reference. A test for linear trend across categories was conducted by entering the categorical variable as an ordinal variable in the proportional hazards regression model. Age was used as time-scale, with the age at enrolment defined as entry time and the age at VTE or censoring defined as exit time. The analyses were performed in three models. Model 1 included age (time scale) and sex, model 2 included model 1 + BMI, and model 3 included model 2 + history of CVD and cancer. There were 44 participants with missing information on BMI, and these were omitted from multivariable analyses only. HRs were estimated for the total study population, and for subgroups stratified by age at inclusion (<65 or ≥65 years). Percentage changes in HRs between models were calculated with the formula: $([HR_{adjusted} - HR_{unadjusted}]/[HR_{unadjusted} - 1]) \times 100\%$ [37]. The proportional hazards assumption was evaluated and verified on the basis of Schoenfeld residuals using a global test. Statistical interactions between physical activity and BMI (physical activity*BMI) and sex (physical activity*sex) were tested by including the cross-product terms separately in the multivariable adjusted proportional hazard model, and no interactions were found.

The population attributable fraction, which is the proportion of VTE events in the study population attributed to inactivity, was calculated from IRs of VTE in the general population (IR_p) and in the physically active population (IR_a), by the formula $([IR_p - IR_a]/[IR_p]) \times 100\%$ [13]. Calculations were done for the total study population and separately for those aged <65 years and ≥65 years.

The total, direct and indirect (mediated by BMI) effects of physical activity on the risk of VTE were quantified on basis of the Aalen additive hazard model [38]. This method provides an estimate of the absolute differences in risk per unit time with 95% CI for a given change in exposure status (e.g., inactive to active), which can be divided into a part attributed to a direct pathway and a part attributed to an indirect pathway.

Statistical analyses were performed with STATA version 15.0 (Stata Corp, College Station, TX, USA) and R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set as 0.05.

Results

Mean age at inclusion was 47 ± 15 years and 52.4% of the participants were women. During 341 451 person-years of follow-up (mean duration per observation period was 6.8 ± 1.6 years), there were 531 incident VTE events yielding a crude incidence rate of 1.56 per 1000 person-years (95% CI 1.43-1.69). Baseline characteristics across categories of physical activity are shown in Table 1. Although the proportion of inactive was similar in men and women, active women were more likely to engage in light physical activity and active men in hard physical activity. Further, individuals participating in hard physical activity were younger, had a more favorable cardiovascular risk profile and were less likely to have a history of CVD and cancer, compared to those in the other categories.

Characteristics of the VTE events are presented in Table 2. Mean age at incident VTE was 68 ± 12 years. The most common clinical presentation was DVT, accounting for 59% of the cases, while the remaining 41% presented as PE with or without concurrent DVT. Further, 60% of the events were classified as provoked, and cancer was the most common provoking factor, accounting for 26% of the cases.

Total and age-stratified IRs and HRs for VTE by the five categories of weekly physical activity are shown in Table 3. In the age- and sex-adjusted model, there was a significant trend of a lower risk of VTE across activity categories (p=0.008). However, the largest decrease in risk (22% lower risk) occurred between the two lowest activity categories (from 'no activity' or '<1 hour/week' to '1-3 hours/week of light activity') and the confidence intervals of the risk estimates for the remaining categories largely overlapped. The risk estimates were attenuated after adjustment for BMI (16% lower risk), while adjustment for history of CVD and cancer did not further influence the risk estimates. Analyses stratified by age at baseline (<65 or ≥65 years) revealed that the association was most pronounced in those aged ≥65. Here, there was a significant trend of a lower risk of VTE across categories of physical activity (p 0.004), which remained statistically significant after adjusting for BMI and history of CVD and cancer. Again, the largest difference in risk estimate (22-27% lower risk)

occurred between the two lowest categories, with overlapping confidence intervals for the remaining categories.

Total and age-stratified IRs and HRs for VTE according to activity status are shown in Table 4. In the age- and sex-adjusted model, active individuals had 23% lower risk of VTE (HR 0.77, 95% CI 0.61-0.92) compared to inactive. The risk estimate was attenuated when adjusting for BMI (16% lower risk), while adjusting for history of CVD and cancer did not further modify the association. In those ≥65 years, physical activity was associated with a 30% lower risk of VTE (HR 0.70, 95% CI 0.55-0.88). The association was attenuated, but still significant, when adjusting for BMI and history of CVD and cancer (25% and 24% lower risk, respectively). In those <65 years, physical activity was associated with 15% lower risk, but the risk estimate was not statistically significant (HR 0.85, 95% CI 0.64-1.13). The proportion of VTE events attributable to physical inactivity was 12.2%, 6.0% and 12.5% for the total study population, in those <65 years and in those ≥65 years, respectively.

Separate analyses for unprovoked and provoked VTE are shown in Table 5 and in Table S2. For both outcomes, the risk estimates suggested a beneficial effect of participating in physical activity, with the largest effect sizes observed in those ≥65 years and in relation to provoked events. Elderly who were physically active had a 34% lower risk of provoked VTE (HR 0.66, 95% CI 0.50-0.89) compared to those who were inactive, and the association remained significant after adjusting for BMI and history of CVD and cancer (28% and 27% lower risk, respectively). There was also a trend of a lower risk of unprovoked VTE in those ≥65 years (HR 0.76, 95% CI 0.52-1.13). Further, we performed analyses separately for PE and DVT (Table 6 and Table S3). In those aged ≥65, physical activity was associated with a lower risk of PE (HR 0.69, 95% CI 0.48-0.98) and DVT (HR 0.70, 95% CI 0.52-0.96), which was attenuated when adjusting for BMI. In those <65 years, there was a trend of a beneficial association in relation to PE (HR 0.67, 95% CI 0.43-1.04), but not DVT (HR 1.00, 95% CI 0.69-1.45).

The total, direct and indirect (mediated via BMI) effects of physical activity on VTE risk derived from the Aalen additive hazard model are shown in Table 7. Overall, the absolute risk

difference between active and inactive was -0.42 (95% CI -0.73 to -0.14) per 1 000 at risk annually, of which 23% (95% CI 11-68) was attributed to BMI. The corresponding differences in risks in those <65 and ≥65 years were -0.20 (-0.42 to -0.07) and -1.59 (-2.74 to -0.52) per 1 000 persons at risk per year, respectively. A relatively larger proportion of the effect was mediated via BMI in those aged <65 (36 %, 95% CI 15-90) than those aged ≥65 (14%, 95% CI 5-48).

Discussion

Our main findings were that (i) there was an inverse association between participation in physical activity and VTE risk, but not in a dose-dependent manner; (ii) a moderate proportion of the association was mediated via BMI-related pathways; and (iii) the association was strongest in those aged ≥65 years and in relation to provoked events.

Whether habitual physical activity influences the risk of VTE has been the focus of several investigations, and diverging results have been reported. Our findings, along with results from three previously published cohort studies, suggest that a moderate amount of physical activity may lower the risk of VTE [16-18]. In the ARIC Study, more than 15 000 middle-aged adults were followed for an average of 15.5 years, and physical activity was reassessed once during follow-up [16]. Individuals in activity categories 2-4, assessed with the Baecke sports questionnaire, had 19-31% lower risk of VTE compared to those in category 1 [16]. Likewise, in the REGARDS Study, participation in physical activity 1-3 times and ≥4 times per week was associated with 30% and 41% lower risk of VTE, respectively, compared to no activity [17]. In the Million Women Study, a cohort of 1.1 million middle-aged women, those reporting at least some weekly physical activity had 4-18% lower risk of VTE, compared to those who were inactive [18].

We previously reported on the association between moderate and high intensity physical activity assessed at the time of inclusion and the risk of incident VTE in the Tromsø Study [23]. Almost 25 000 participants were followed for a median of 12.5 years, and no association was observed between physical activity and VTE risk. In traditional prospective studies with exposure

status recorded at baseline only, modifiable risk factors, such as physical activity, represent a challenge [28, 29]. Participants who change behavior during follow-up will be misclassified (non-differential), which typically leads to regression dilution and underestimation of the true association [28]. In the present study, we were able to address this challenge because exposure status was updated for those who took part in several surveys, and the duration of each observation period was kept relatively short (<7 years). This is likely to reduce regression dilution bias, and may, in addition to increased power, explain why the present findings differ from our previous report.

In the present study, the largest difference in risk was observed between the inactive and the lowest activity category, with modest additional benefits of higher amounts of physical activity. This is in line with previous findings [16, 18], and indicates that avoiding an inactive lifestyle may be sufficient to lower the risk of VTE. It also coheres with the fact that immobility and other circumstances associated with physical restriction are strongly associated with an elevated VTE risk [39-42]. At the other extreme, it has been suggested that high amounts of strenuous physical activity may increase the risk of VTE [18, 22]. Specifically, in the CHS, a cohort of adults aged ≥65 years, participation in strenuous physical activity was associated with a 75% higher risk of VTE compared to being inactive [22]. In contrast, our findings suggested that the beneficial effect of physical activity was largely restricted to those aged ≥65 years. The diverging results may be explained by different assessment and categorization of physical activity, as the beneficial effect in our study applied to physical activity in general, while the harmful effect in the CHS was restricted to strenuous activity.

We found that active individuals aged ≥65 had 30% lower risk of VTE compared to those who were inactive, and that 12.5% of VTE events in this population could be attributed to inactivity. When expressed in the additive hazard model, this translated into an annual difference in absolute risk of 1.6 per 1000. Alongside the high prevalence of physical inactivity [43], this suggests that a successful population strategy to reduce inactivity could have a notable impact on the incidence of VTE, particularly in the elderly. Although VTE may occur in people of all ages, it is relatively uncommon among young individuals [2]. Due to their low baseline risk, it is plausible that several

strong risk factors need to be present simultaneously to exceed the thrombosis threshold. Accordingly, the potential risk modification obtained with physical activity may be too small to elicit a detectable effect in young individuals. Further, in those ≥65 years, the lower risk, particularly of provoked events, may be partly mediated by a lower incidence of VTE-associated diseases. Although our multivariable adjusted analyses showed that history of CVD and cancer did not modify the risk estimates, the potential of residual confounding remains.

Obesity is a well-recognized risk factor for VTE [44, 45], and BMI is usually treated as a confounding variable in analyses of the association between physical activity and VTE risk [16, 18, 23, 24]. In our study, the risk estimates were attenuated by 12% in young adults and 7% in the elderly when BMI was added to the regression models. However, as physical activity is important in weight maintenance [12, 31], it is reasonable to consider BMI as an intermediate in the causal pathway between physical activity and VTE. By applying the Aalen additive hazard model, we showed that a low to moderate proportion of the total effect of physical activity on VTE risk was mediated by BMI. Thus, although BMI-related pathways mediated some of the effect, our findings suggest that the beneficial effect of physical activity on VTE risk may primarily be ascribed to other mechanisms than those associated with weight status.

The main strengths of the present study include a large number of participants recruited from a general population, high participation rates, wide age distribution, prospective design with repeated measurements for a part of the study population, and thoroughly validated 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 also the first study to apply mediation analyses to quantify the role of BMI as a mediator in the relationship between physical activity and VTE. Some limitations of the study need to be considered. The analyses were restricted to participants who had provided information on their physical activity habits (99% of the participants), and the responders may differ from the non-responders (1% of the participants). 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). However, as exposure data was collected prior to the occurrence of potential disease, such misclassification is likely independent of the outcome and not a threat to the internal validity of the study. Still, objective assessment strategies (e.g., cardiorespiratory fitness) have a higher level of precision and are reported to be superior predictors of all-cause and cancer-related mortality [46, 47]. Interestingly, an association between cardiorespiratory fitness in early adulthood and future risk of unprovoked VTE was reported in a recent study [48]. 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 showed meaningful associations with cardiometabolic markers, which supports the validity of the variable. Finally, as measures of physical activity and BMI used in the mediation analysis were assessed cross-sectionally, the temporal sequence is unknown, and the results must be interpreted under the assumption that BMI is at least partly determined by physical activity [31].

In conclusion, we found that weekly participation in physical activity was associated with lower the risk of incident VTE, particularly in participants aged ≥65 years and for provoked events. The association was only partly mediated by BMI, and appeared to be independent of history of CVD and cancer. Future studies applying objective assessment strategies of physical activity and physical fitness are warranted to confirm the association.

Addendum

L. H. Evensen analyzed the data and drafted the manuscript. T. Isaksen collected data and revised the manuscript. K. Hindberg provided statistical support. 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 Journal of Thrombosis and Haemostasis by all authors.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Tables and figures

Table 1 Baseline characteristics of participants (n= 30 002) across categories of weekly physical activity. The Tromsø Study (1994-2016)

	Inactive*	1-3 h light PA†	>3 h light PA†	1-3 h hard PA‡	>3 h hard PA‡
Number of participants	7237	7148	6170	6309	3138
Age, years	50 (16)	47 (14)	50 (16)	42 (12)	41 (12)
Sex (women)	52.3 (3787)	58.5 (4181)	60.5 (3733)	47.1 (2974)	34.6 (1087)
BMI, kg/m^2	26.0 (4.4)	25.4 (4.0)	25.1 (3.8)	24.9 (3.5)	24.7 (3.2)
Triglycerides, mmol/L	1.71 (1.15)	1.57 (1.04)	1.50 (0.97)	1.45 (0.99)	1.44 (1.02)
Total cholesterol, mmol/L	6.14 (1.36)	6.09 (1.30)	6.15 (1.33)	5.69 (1.19)	5.64 (1.18)
HDL cholesterol, mmol/L	1.45 (0.40)	1.50 (0.41)	1.54 (0.42)	1.49 (0.40)	1.50 (0.41)
Systolic blood pressure, mmHg	136 (23)	134 (20)	136 (22)	130 (18)	131 (17)
Smoking	40.1 (2899)	37.6 (2685)	36.6 (2258)	30.4 (1916)	29.3 (920)
Higher education§	23.6 (1696)	29.1 (2074)	28.8 (1765)	45.4 (2964)	41.3 (1292)
History of CVD	9.6 (692)	6.2 (440)	8.0 (491)	2.7 (171)	2.7 (85)
History of cancer	3.7 (269)	2.8 (199)	3.6 (224)	1.9 (117)	1.6 (49)

BMI body mass index, *CVD* cardiovascular disease (angina pectoris, stroke, myocardial infarction), *h* hours, *HDL* high-density lipoprotein, *PA* physical activity

*Less than 1 h of physical activity per week

†Activity at an intensity **not causing** breathlessness and sweating

‡Activity at an intensity **causing** breathlessness and sweating

§≥15 years of education (corresponding to 3 years in university or academy)

Values are mean (standard deviation) or percentage (count)

Table 2 Characteristics of VTE events (n=531). The Tromsø Study (1994-2016)

	% (n)
Age, years (mean, SD)	68 (12)
Sex (women)	50.1 (266)
Clinical characteristics	
Pulmonary embolism	40.7 (216)
Deep vein thrombosis	59.3 (315)
Provoked	60.5 (321)
Unprovoked*	39.5 (210)
Provoking factors†	
Surgery	18.3 (97)
Trauma	8.5 (45)
Acute medical condition	12.8 (68)
Cancer	26.2 (139)
Immobilization‡	17.0 (90)
Other§	5.3 (28)
Clinical risk factors	
Estrogens (HRT, oral contraceptives)	4.9 (26)
Heredity¶	2.8 (15)
Pregnancy/postpartum	0.8 (4)
Other medical conditions**	21.9 (100)

HRT hormone replacement therapy, *SD* standard deviation, *VTE* venous thromboembolism

*No provoking factors at the time of diagnosis

†One patient may have multiple provoking factors

‡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)

¶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)

Values are percentage (count) unless otherwise noted

Table 3 Age-stratified incidence rates and hazard ratios with 95% confidence intervals for total VTE by categories of weekly physical activity. The Tromsø Study (1994-2016)

	Person-years	VTE events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR Model 2 (95% CI)‡	HR Model 3 (95% CI)§
All						
Inactive	92 765	190	2.05 (1.78-2.36)	1.00	1.00	1.00
Light PA 1-3 h	72 979	111	1.52 (1.27-1.83)	0.78 (0.62-0.99)	0.84 (0.66-1.06)	0.84 (0.66-1.06)
Light PA >3 h	59 092	107	1.81 (1.50-2.19)	0.80 (0.63-1.01)	0.89 (0.70-1.14)	0.89 (0.70-1.14)
Hard PA 1-3 h	81 534	88	1.08 (0.88-1.33)	0.74 (0.58-0.96)	0.81 (0.63-1.05)	0.82 (0.63-1.06)
Hard PA >3 h	35 082	35	1.00 (0.72-1.39)	0.69 (0.48-0.99)	0.77 (0.54-1.12)	0.79 (0.55-1.13)
p for trend				0.008	0.084	0.101
Age <65 years						
Inactive	71 402	71	0.99 (0.79-1.25)	1.00	1.00	1.00
Light PA 1-3 h	56 236	44	0.78 (0.58-1.06)	0.84 (0.57-1.22)	0.91 (0.63-1.33)	0.91 (0.62-1.33)
Light PA >3 h	41 448	35	0.84 (0.60-1.18)	0.86 (0.60-1.29)	0.97 (0.65-1.47)	0.96 (0.64-1-45)
Hard PA 1-3 h	71 506	57	0.80 (0.61-1.03)	0.91 (0.64-1.29)	1.00 (0.52-1.44)	1.01 (0.71-1.43)
Hard PA >3 h	30 428	19	0.62 (0.40-0.98)	0.75 (0.45-1.24)	0.87 (0.52-1.44)	0.87 (0.52-1.45)
p for trend				0.372	0.83	0.85
Age ≥65 years						
Inactive	21 363	119	5.57 (4.65-6.67)	1.00	1.00	1.00
Light PA 1-3 h	16 742	67	4.00 (3.15-5.08)	0.73 (0.54-0.99)	0.78 (0.57-1.05)	0.78 (0.58-1.06)

Light PA >3 h	17 644	72	4.08 (3.24-5.14)	0.74 (0.55-0.99)	0.81 (0.60-1.09)	0.81 (0.60-1.09)
Hard PA 1-3 h	10 029	31	3.09 (2.17-4.40)	0.58 (0.39-0.87)	0.63 (0.42-0.94)	0.63 (0.42-0.95)
Hard PA >3 h	4654	16	3.44 (2.11-5.61)	0.64 (0.38-1.08)	0.70 (0.41-1.19)	0.72 (0.42-1.22)
p for trend				0.004	0.022	0.027

CI confidence interval, *h* hour, *HR* hazard ratio, *IR* incidence rate*, PA* physical activity, *VTE* venous thromboembolism

*Per 1000 person-years

†Adjusted for age (as timescale) and sex

‡Model 1 + body mass index

§Model 2 + history of cardiovascular disease and cancer

Table 4 Total and age-stratified incidence rates and hazard ratios with 95% confidence intervals for total VTE by physical activity status. The Tromsø Study (1994-2016)

	Person-years	VTE events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR Model 2 (95% CI)‡	HR Model 3 (95% CI)§
All						
Inactive¶	92 765	190	2.05 (1.78-2.36)	1.00	1.00	1.00
Active**	248 687	341	1.37 (1.23-1.52)	0.77 (0.64-0.92)	0.84 (0.70-1.01)	0.84 (0.70-1.01)
Age <65 years						
Inactive¶	71 402	71	0.99 (0.78-1.25)	1.00	1.00	1.00
Active**	199 618	155	0.78 (0.66-0.91)	0.85 (0.64-1.13)	0.95 (0.71-1.26)	0.95 (0.71-1.26)
Age ≥65 years						
Inactive¶	21 363	119	5.57 (4.65-6.67)	1.00	1.00	1.00
Active**	49 068	186	3.79 (3.28-4.38)	0.70 (0.55-0.88)	0.75 (0.59-0.95)	0.76 (0.60-0.96)

CI confidence interval, *HR* hazard ratio, *IR* incidence rate*, VTE* venous thromboembolism

*Per 1000 person-years

†Adjusted for age (as timescale) and sex

‡Model 1 + body mass index

§Model 2 + history of cardiovascular disease and cancer

¶<1 hour/week of physical activity

**≥1 hour/week of physical activity

Table 5 Overall and age-stratified incidence rates and hazard ratios with 95% confidence intervals for unprovoked and provoked VTE by physical activity status. The Tromsø Study (1994-2016)

	Person-years	VTE events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR Model 2 (95% CI)‡	HR Model 3 (95% CI)§
PROVOKED VTE						
All						
Inactive¶	92 765	118	1.27 (1.06-1.52)	1.00	1.00	1.00
Active**	248 687	203	0.82 (0.71-0.94)	0.74 (0.59-0.93)	0.80 (0.64-1.01)	0.81 (0.64-1.02)
Age <65 years						
Inactive¶	71 402	40	0.56 (0.41-0.76)	1.00	1.00	1.00
Active**	199 618	86	0.43 (0.35-0.53)	0.84 (0.58-1.22)	0.92 (0.63-1.34)	0.92 (0.63-1.34)
Age ≥65 years						
Inactive¶	21 363	78	3.65 (2.92-4.56)	1.00	1.00	1.00
Active**	49 068	117	2.38 (1.99-2.86)	0.66 (0.50-0.89)	0.72 (0.54-0.97)	0.73 (0.54-0.98)
UNPROVOKED VTE						
All						
Inactive¶	92 765	72	0.78 (0.62-0.98)	1.00	1.00	1.00
Active**	248 687	138	0.55 (0.47-0.66)	0.81 (0.61-1.08)	0.90 (0.67-1.21)	0.91 (0.68-1.21)
Age <65 years						
Inactive¶	71 402	31	0.43 (0.31-0.62)	1.00	1.00	1.00
Active**	199 618	69	0.35 (0.27-0.44)	0.88 (0.57-1.34)	0.99 (0.65-1.53)	0.99 (0.64-1.52)
Age ≥65 years						
Inactive¶	21 363	31	1.92 (1.41-2.61)	1.00	1.00	1.00
Active**	49 068	69	1.41 (1.11-1.78)	0.76 (0.52-1.13)	0.82 (0.55-1.22)	0.82 (0.55-1.22)

CI confidence interval, *HR* hazard ratio, *IR* incidence rate*, VTE* venous thromboembolism

*Per 1000 person-years

†Adjusted for age (as timescale) and sex

‡Model 1 + body mass index

§Model 2 + history of cardiovascular disease and cancer

¶<1 hour/week of physical activity

**≥1 hour/week of physical activity

Table 6 Overall and age-stratified incidence rates and hazard ratios with 95% confidence intervals for PE and DVT by physical activity status. The Tromsø Study (1994-2016)

	Person-years	VTE events	Crude IR (95% CI)*	HR model 1 (95% CI)†	HR Model 2 (95% CI)‡	HR Model 3 (95% CI)§
PULMONARY EMBOLISM						
All						
Inactive¶	92 765	83	0.89 (0.73-1.11)	1.00	1.00	1.00
Active**	248 687	133	0.53 (0.45-0.63)	0.69 (0.52-0.91)	0.77 (0.58-1.02)	0.77 (0.58-1.02)
Age <65 years						
Inactive¶	71 402	32	0.45 (0.32-0.63)	1.00	1.00	1.00
Active**	199 618	53	0.27 (0.20-0.35)	0.67 (0.43-1.04)	0.77 (0.49-1.20)	0.76 (0.49-1.19)
Age ≥65 years						
Inactive¶	21 363	51	2.39 (1181-3.14)	1.00	1.00	1.00
Active**	49 068	80	1.63 (1.31-2.03)	0.69 (0.48-0.98)	0.76 (0.53-1.09)	0.76 (0.53-1.09)
DEEP VEIN THROMBOSIS						
All						
Inactive¶	92 765	107	1.15 (0.95-1.39)	1.00	1.00	1.00
Active**	248 687	208	0.84 (0.73-0.96)	0.82 (0.65-1.04)	0.89 (0.70-1.14)	0.90 (0.71-1.14)
Age <65 years						
Inactive¶	71 402	39	0.55 (0.40-0.75)	1.00	1.00	1.00
Active**	199 618	102	0.51 (0.42-0.62)	1.00 (0.69-1.45)	1.10 (0.75-1.59)	1.10 (0.76-1.60)
Age ≥65 years						
Inactive¶	21 363	68	3.18 (2.05-4.04)	1.00	1.00	1.00
Active**	49 068	106	2.16 (1.79-2.61)	0.70 (0.52-0.96)	0.75 (0.54-1.03)	0.76 (0.55-1.04)

CI confidence interval, *DVT* deep vein thrombosis, *HR* hazard ratio, *IR* incidence rate*, PE* pulmonary embolism

*Per 1000 person-years

†Adjusted for age (as timescale) and sex

‡Model 1 + body mass index

§Model 2 + history of cardiovascular disease and cancer

¶<1 hour/week of physical activity

**≥1 hour/week of physical activity

Table 7 Total, direct and indirect (mediated via body mass index) effects of physical activity status on the risk of VTE derived from the Aalen additive hazard model. The Tromsø Study (1994-2016)

	Direct effect (95% CI) x 10^{-3}*†	Indirect effect (95% CI) x 10^{-3}*†	Total effect (95% CI) x 10^{-3}*†	Indirect/total effect (95% CI)
All				
Active‡ versus inactive§	-0.32 (-0.64 to 0.006)	-0.10 (-0.13 to -0.06)	-0.42 (-0.73 to -0.14)	0.23 (0.11 to 0.68)
Age <65 years				
Active‡ versus inactive§	-0.07 (-0.33 to 0.20)	-0.07 (-0.10 to -0.04)	-0.20 (-0.42 to -0.07)	0.36 (0.15 to 0.90)
Age ≥65 years				
Active‡ versus inactive§	-1.35 (-2.54 to -0.16)	-0.22 (-0.37 to -0.09)	-1.59 (-2.74 to -0.52)	0.14 (0.05 to 0.48)

CI confidence interval, *VTE* venous thromboembolism

*Per year

†Adjusted for age (as timescale) and sex

‡≥1 hour/week of physical activity

§<1 hour/week of physical activity

Fig. 1. Overview of study participation (dots) and observation periods (arrows). In total, 30 002 individuals were included in the study. Of these, 18 064 participated in one survey, 8541 participated in two surveys and 3397 participated in three surveys.