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Physical activity, cardiorespiratory fitness and venous thromboembolism

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Summary

Venous thromboembolism (VTE) is the third most common lethal cardiovascular disease (CVD) after myocardial infarction and stroke. Individuals with VTE are at risk of adverse consequences such as recurrence and premature mortality, and the disease represents a growing public health concern. Identification of modifiable risk factors is currently a priority to curb the increasing burden of VTE. Although physical activity and cardiorespiratory fitness (CRF) are associated with a wealth of health benefits including lower risk of arterial CVD, their associations with VTE remain to be established. The aim of the present thesis was to summarize the existing knowledge on this topic and to identify important knowledge gaps. Further, we aimed to study the associations between physical activity and CRF and the risk of incident VTE, and to explore to what extent a potential association was explained by body weight status. Finally, we wanted to investigate whether physical activity was associated with the risk of recurrent disease and mortality after VTE.

The present thesis comprises four scientific papers, and is based on data from the Tromsø Study surveys 4 to 6. At each survey, participant information was collected via self-administered questionnaires, physical examinations and blood samples. Information on physical activity was collected from the questionnaires, and CRF was estimated from physical activity as well as other physical variables. Participants were followed from the date of inclusion until the date of an incident VTE (in Paper IV: to a recurrent VTE), migration, death or the end follow-up.

In Paper I, we concluded that the literature on physical activity and VTE was diverging, but suggestive of a beneficial role of physical activity. We proposed that future studies should account for fluctuations in activity levels during follow-up by repeated measurement analysis and explore body mass index (BMI) as a potential mediator. We also requested studies using objective assessment strategies. In Paper II, we reported that physical activity was associated with a lower risk of incident VTE, and that only a small to moderate proportion of the association was explained by BMI. In Paper III, we found that higher estimated CRF also was associated with a lower VTE risk, and these effect sizes were larger than for physical activity. Finally, Paper IV revealed that physical activity was associated with a lower risk of mortality after incident VTE, but did not influence recurrence risk.

Our results imply that regular physical activity and CRF are modifiable targets for primary prevention of VTE and improved prognosis after VTE.

Sammendrag

Venøs tromboembolisme (VTE) er den tredje vanligste hjerte- og karsykdommen etter hjerteinfarkt og hjerneslag. Personer med VTE risikerer uheldige konsekvenser som residiv og tidlig død, og sykdommen representerer et økende folkehelseproblem. Identifisering av modifiserbare risikofaktorer er for tiden en prioritet. Selv om fysisk aktivitet og kardiorespiratorisk form er assosiert med mange helsemessige fordeler, inkludert lavere risiko for arteriell hjerte-kar-sykdom, så er det fortsatt uklart om det også påvirker risikoen for VTE. Målet med denne avhandlingen var å oppsummere eksisterende kunnskap om dette emnet og å identifisere kunnskapshull. Videre hadde vi som mål å studere sammenhengen mellom fysisk aktivitet og kardiorespiratorisk form og risikoen for VTE, og å utforske i hvilken grad en potensiell assosiasjon kunne forklares av kroppsvekt. Til slutt ønsket vi å undersøke om fysisk aktivitet var assosiert med risiko for residiv av VTE og dødelighet etter VTE.

Avhandlingen består av fire vitenskapelige artikler, og er basert på data fra Tromsøundersøkelsen (4 til 6). Ved hver undersøkelse ble informasjon om deltakerne samlet inn via selvadministrerte spørreskjemaer, fysiske undersøkelser og blodprøver. Informasjon om fysisk aktivitet ble hentet fra spørreskjemaene, og kardiorespiratorisk form ble estimert ut fra fysisk aktivitet og andre fysiske variabler. Deltakerne ble fulgt fra inklusjonsdatoen og frem til en eventuell førstegangs VTE (i artikkel IV: til en eventuell residiverende VTE), migrasjon, død eller studieslutt.

I artikkel I konkluderte vi med at litteraturen om fysisk aktivitet og VTE var sprikende, men antydet en gunstig effekt av fysisk aktivitet på VTE risiko. Vi foreslo at fremtidige studier burde ta høyde for svingninger i aktivitetsnivå under oppfølgingen og undersøke i hvilken grad sammenhengen kan forklares av kroppsvekt. Vi etterlyste også studier som bruker objektive målinger av fysisk aktivitet og fysisk form. I artikkel II rapporterte vi at fysisk aktivitet var assosiert med en lavere risiko for VTE, og at dette i liten til moderat grad kunne forklares av kroppsvekt. I artikkel III fant vi at høyere kardiorespiratorisk form også var assosiert med en lavere VTE risiko, og disse effektstørrelsene var større enn for fysisk aktivitet. Til slutt, i artikkel IV fant vi at fysisk aktivitet var assosiert med en lavere risiko for dødelighet etter VTE, men at risikoen for residiv ikke var påvirket.

Resultatene våre antyder at fysisk aktivitet og kardiorespiratorisk form utgjør potensielle angrepspunkt for primær forebygging av VTE og forbedret prognose etter VTE.

List of papers

The thesis is based on the following papers:

I **Regular Physical Activity and Risk of Venous Thromboembolism**

Evensen LH, Brækkan SK, Hansen JB

Semin Thromb Hemost. 2018 Nov;44(8):765-779

II **Repeated assessments of physical activity and risk of incident venous thromboembolism**

Evensen LH, Isaksen T, Hindberg K, Brækkan SK, Hansen JB

J Thromb Haemost. 2018 Nov;16(11):2208-2217

III **Cardiorespiratory fitness and future risk of venous thromboembolism**

Evensen LH, Isaksen T, Brækkan SK, Hansen JB

J Thromb Haemost. 2019 Aug 25. [Epub ahead of print]

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

Evensen LH, Isaksen T, Brækkan SK, Hansen JB

J Thromb Haemost. 2019 Jun;17(6):901-911

Abbreviations

APC	activated protein C
ARIC	The Atherosclerosis Risk in Communities Study
AT	antithrombin
BMI	body mass index
CHS	The Cardiovascular Health Study
CI	confidence interval
COC	combined oral contraceptive
CRF	cardiorespiratory fitness
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	cardiovascular disease
DCH	The Danish Cancer and Health Study
DVT	deep vein thrombosis
eCRF	estimated cardiorespiratory fitness
EV	extracellular vesicle
F	factor
FVL	factor V Leiden
GWAS	genome wide association studies
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
HRT	hormone replacement therapy
HUNT	The Nord-Trøndelag Health Study
ICD	International Classification of Diseases
IPAQ	International Physical Activity Questionnaire
IWHS	Iowa Women's Health Study
KIHD	The Kuopio Ischaemic Heart Disease Risk Factors Study
LITE	The Longitudinal Investigation of Thromboembolism Etiology
MEGA	The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study

MESA	The Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
NHS	Nurses´ Health Study
PAI-1	plasminogen activator inhibitor-1
PE	pulmonary embolism
PTS	post-thrombotic syndrome
RCT	randomized controlled trial
REGARDS	The Reasons for Geographical and Racial Differences in Stroke Study
SD	standard deviation
SHR	sub-distribution hazard ratio
TF	tissue factor
TFPI	tissue factor pathway inhibitor
UNN	The University Hospital of North Norway
VTE	venous thromboembolism
vWF	von Willebrand factor
WHO	World Health Organization

1 Introduction

Non-communicable diseases represent a major global health challenge of the 21st century, and cardiovascular diseases (CVDs) are main contributors. The World Health Organization (WHO) has set a global target of 25% relative reduction in premature mortality from non-communicable diseases by 2025.[1]

Among fatal CVDs, venous thromboembolism (VTE) is the third most common after coronary heart disease and stroke.[2] VTE comprises two disease entities, deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to the formation of a blood clot in the deep veins, most often of the lower extremities. Patients with DVT typically present with symptoms such as pain, edema, redness and increased temperature of the affected extremity. Traditionally, PE was considered a complication of DVT, where a part of the clot dislodges, travels with the blood stream through the right side of the heart and ultimately obstructs a pulmonary artery. However, a large number of PEs occur in the absence of a detectable DVT, and the contemporary understanding of PE additionally includes cardiac thrombus origin and *de novo* formation in the lungs.[3] Symptoms compatible with PE are dyspnea, tachypnea, pleuritic chest pain, coughing, and in severe instances, circulatory collapse and death.

The importance of physical activity for health has been valued since ancient times, and mounting evidence convincingly show that physical activity is associated with a lower risk of arterial CVDs, type-2 diabetes, some cancers, and premature mortality.[4] Insufficient physical activity is recognized as the fourth leading cause of death, and accountable for 3.2 million deaths worldwide each year (2010).[5] Nevertheless, the current levels of physical activity are probably the lowest in human history, and physical inactivity has been referred to as a global pandemic.[6,7]

The health benefits associated with an active lifestyle are undoubtedly extensive. However, the relationship between physical activity and the risk of VTE remains to be established.[2,8] There is also a need to explore the role of physical activity in relation to recurrence and mortality after incident VTE. Such knowledge may contribute to improved risk stratification, prevention and potentially reduce the burden of VTE.

The present thesis focuses on the association between physical activity and the risk of incident VTE and VTE related complications.

1.1 Epidemiology of venous thromboembolism

VTE is a common disease with an annual incidence of 1 to 2 per 1000 in adult populations[9-11], and it is estimated that there are 10 million in-hospital events worldwide annually.[12] The incidence of VTE is strongly dependent on age, and increases from less than one per 1000 in those aged <50 years to more than 8 per 1000 in those aged >80 years.[13] During childbearing years, the incidence is higher in women compared with men of the same age, whereas men have a higher incidence in the older age groups.[9,13] DVT is the most common clinical manifestation of VTE, accounting for two thirds of all events, and the remaining present as PE with or without concurrent DVT.[14] Approximately one third of patients with DVT have a clinically silent PE[15], and more than half of all patients with PE have a silent or symptomatic DVT.[16,17]

A distinction is made between VTE events that occur in the presence of a provoking factor and those that are apparently unprovoked. Provoking factors can either be transient (e.g., surgery, trauma, hospitalization) or persistent (e.g., cancer, inflammatory bowel disease) risk factors.[18] When no such factor can be identified, the event is classified unprovoked.[18] Data from population-based studies suggest that 50 to 60% of all VTE events are provoked.[10,19] The classification into provoked and unprovoked VTE not only influences the treatment strategy, but also has important prognostic impact.[20]

Patients with VTE are at risk of serious short- and long-term complications. PE is the most lethal manifestation of VTE, and it is estimated that almost 25% of all PEs present as sudden death.[21] The overall one-month mortality risk after VTE is 6 to 11%[9,10,22], and is twice as high after PE compared with isolated DVT.[9,22] This difference diminishes with time, and the overall one- and five-year mortality risks are 17 to 23%[9,22,23] and 40 to 46%[24,25], respectively. The mortality risk is higher in patients with provoked than in those with unprovoked VTE, potentially due to higher age and more comorbidities.[22,24] When compared with the general population, individuals with a history of VTE remain at higher risk of mortality for up to 3 decades after the initial event.[25,26]

Although anticoagulant treatment efficiently treats acute VTE, recurrences are frequent. The risk of recurrence peaks during the first year after the initial event (7 to 13%), and the cumulative recurrence is 30 to 40% after 10 years.[24,27,28] The recurrence risk is highest among patients with VTE provoked by a persistent risk factor, intermediate in those with unprovoked VTE and lowest in those with VTE provoked by a major transient risk factor.[18] The clinical presentation of the incident event predicts the type of a potential recurrent event, and a patient

with incident PE is three times more likely to have a recurrence as PE compared with a patient with incident DVT.[29]

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of PE that occurs in 0.5 to 4% of the patients.[30,31] The pathogenesis is not clearly understood, but hallmarks of the disease are fibrotic transformation of unresolved thrombi, occlusive vascular remodeling and obstruction of pulmonary arteries.[32,33] Patients with CTEPH are burdened with dyspnea, fatigue, chest pain, reduced exercise capacity and signs of right heart failure.[34 30,31] Factors associated with the development of CTEPH are unprovoked PE, previous PE, larger perfusion defects, lupus anticoagulant/antiphospholipid antibodies and elevated coagulation factor (F) VIII.[32]

The post-thrombotic syndrome (PTS) occurs in 20 to 50% of patients with DVT, and manifests with pain, swelling, heaviness and skin changes of the affected extremity.[23,33,35] The underlying situation in PTS is incomplete thrombus resolution, and hallmarks of the syndrome are structural changes in the vessel wall, venous reflux and elevated venous pressure.[33] Risk factors for PTS include recurrent ipsilateral DVT, proximal DVT, older age, higher body mass index (BMI), pre-existing venous insufficiency and inadequate anticoagulant treatment.[35,36]

Despite efforts to improve the prevention of VTE, the incidence has remained stable or slightly increased over the previous decades.[11,37] The persistent incidence may partly result from higher sensitivity of diagnostic methods, but may also indicate that the current strategies for risk stratification and prevention are suboptimal.[11] The burden of VTE is extensive at both the individual and population level, and involves premature death, loss of disability-adjusted life-years, impaired quality of life, and large costs due to healthcare and lost workforce.[26,36,38,39] Consequently, there is a great need for further efforts to advance knowledge of risk factors in order to improve risk stratification, prevention and ultimately reduce the burden of VTE.

1.2 Pathophysiology of venous thromboembolism

The hemostatic system holds vital importance in the management of vascular injury, and delicately balances pro- and anticoagulant activity to maintain blood fluidity under normal physiological conditions. Disturbance of this balance may lead to thrombin generation and clot formation not intended for hemostatic function - *thrombosis*. The framework for understanding the pathophysiology of thrombosis includes changes in the vessel wall (endothelial dysfunction), blood flow (stasis) and blood composition (hypercoagulability), collectively referred to as Virchow's triad (Figure 1).[40,41]

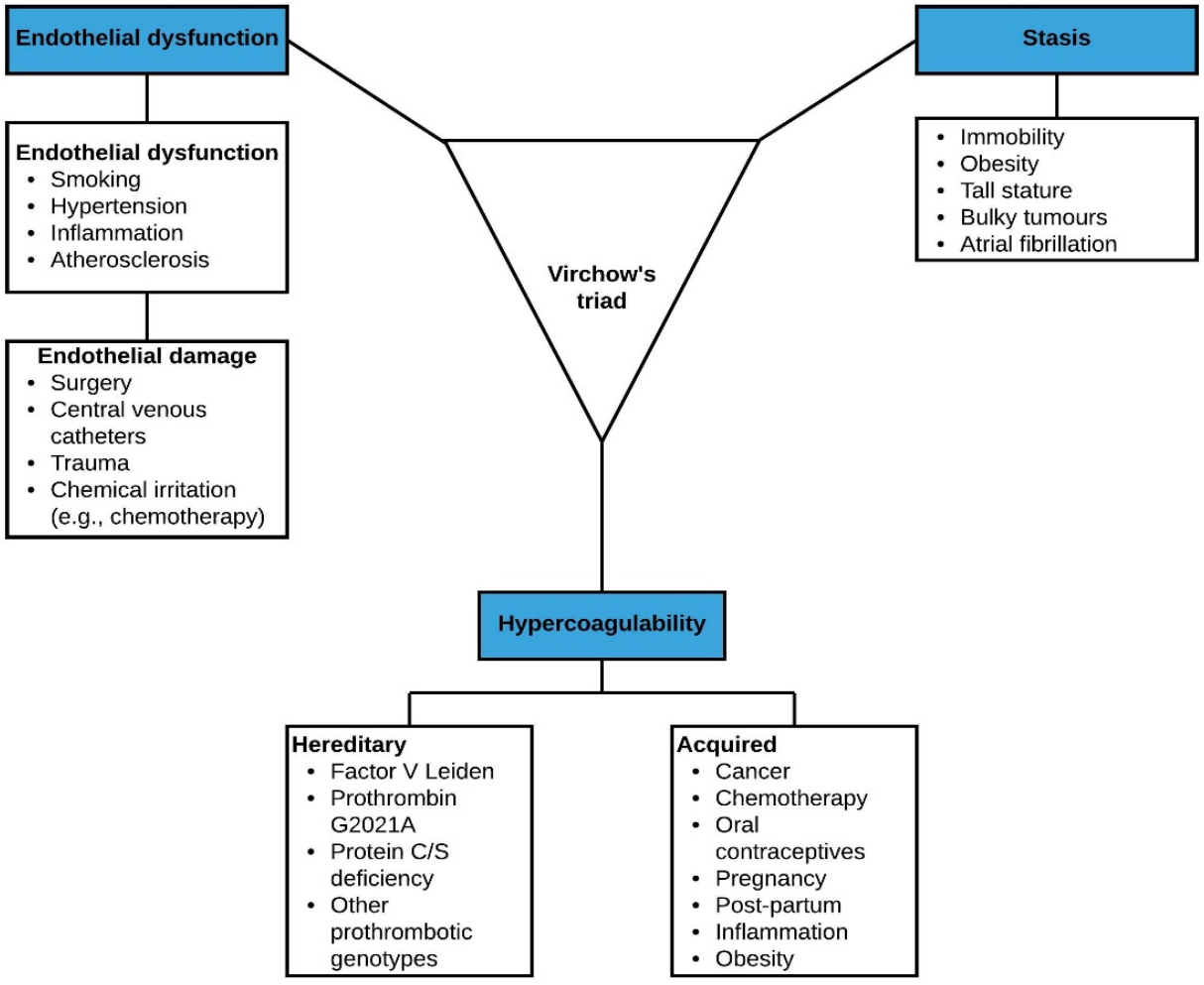

Figure 1 Virchow's triad with categorization of some risk factors for thrombosis

Although vascular injury with exposure of extravascular tissue factor (TF) is the main trigger of the coagulation cascade in vivo, the majority of venous thrombi develop in the presence of intact endothelium.[42-44] Data from autopsy and phlebography studies suggest that non-trauma related venous thrombi primarily develop in the sinuses behind the valves.[41] This is indirectly supported by the observation that DVT occurs more frequently in individuals with a higher number of valves.[45] In the valvular sinuses, the blood flow is characterized by a vortical pattern that is partly separated from the systemic circulation leading to hypoxia (Figure 2).[41] Although the endothelium normally expresses a thromboresistant phenotype[46,47], hypoxia triggers activation of endothelial cells and induces a shift towards a pro-inflammatory and pro-coagulant state.[41,42] Hallmarks of endothelial activation are increased expression of adhesion molecules that bind leukocytes, platelets and TF-positive extracellular vesicles (EVs).[42] Subsequent local coagulation activation may overwhelm the anticoagulant pathways and lead to thrombus formation.[42] The theory on stasis-induced hypoxia with activation of the coagulation cascade is also in coherence with the observed relationship between circumstances associated with physical restriction and stasis (e.g., plaster cast, bed rest and paralysis), and increased risk of VTE.[48-51]

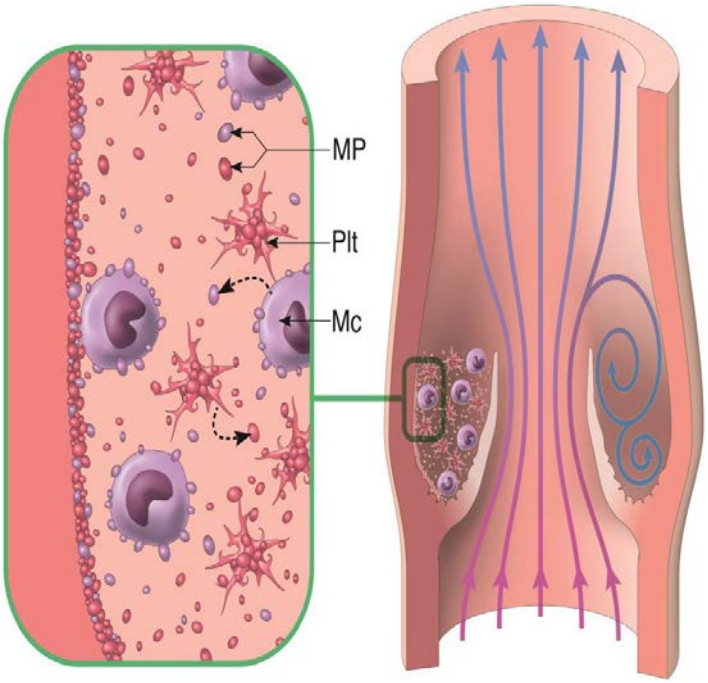

Figure 2 Venous valve sinuses as site of thrombus formation. Hypoxic conditions due to vortical blood flow induces activation of endothelial cells and recruitment of leukocytes, such as monocytes (Mc) and platelets (Plt). Upon activation, these cells bud off TF-positive microparticles (MP), also denoted EVs, contributing to coagulation activation and thrombus formation. (Illustration by Roy Lysså)

Thrombophilia denotes a tendency to clot formation due to a hypercoagulable state, and may be caused by acquired or inherited disorders.[52] A hypercoagulable state may broadly be characterized by two mechanism; loss-of function of anticoagulant proteins or gain-function of procoagulants.[52] Pregnancy represents an example of acquired thrombophilia with a transient increase in levels of FVII, FVIII, FX, fibrinogen, von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1).[53] Likewise, cancer, obesity, surgery and use of hormonal oral contraceptives may represent acquired thrombophilias with procoagulant alterations in the hemostatic system.[42] Inherited thrombophilia relates to genetic variations that induce a hypercoagulable state. Impaired anticoagulant function is exemplified in deficiencies of antithrombin, protein C and protein S, whereas the factor V Leiden (FVL) mutation represents a gain-of-function variant of FV that is resistant to degradation.[52] Inherited thrombophilias are revisited in chapter 1.3.1.

Although PE often occurs as a complication of DVT, a low detection rate of peripheral thrombi in patients with PE has prompted efforts to identify alternative etiological explanations.[3] On basis of observations that heart disease, especially right-sided, was more strongly associated with isolated PE than with DVT, a theory on cardiac thrombus origin has been proposed.[54,55] Potentially, cardiac conditions (e.g., atrial fibrillation) may contribute to the development of right-sided intracardiac thrombi, that enter the pulmonary circulation and obstructs a pulmonary artery.[55] Additionally, in situ thrombus formation within the pulmonary arteries, mediated through hypoxia and/or inflammatory pathways, has also been suggested as a potential pathophysiological mechanism of PE.[3]

1.3 Risk factors for venous thromboembolism

A risk factor can be anything that increases the likelihood of developing a disease. VTE develops in a complex interplay between inherited and acquired risk factors, and multiple coexisting factors are required. The dynamic relationship between risk factors can be explained by the thrombosis potential model (Figure 3).[56] This model illustrates how the thrombosis potential depends on an accumulation of risk factors, and when the natural anticoagulant mechanisms are overwhelmed, the thrombosis threshold is exceeded, resulting in thrombosis. Revisiting Virchow's triad from 1856, it is striking that the currently known risk factors for VTE can be incorporated into this framework (Figure 1).[40,56]

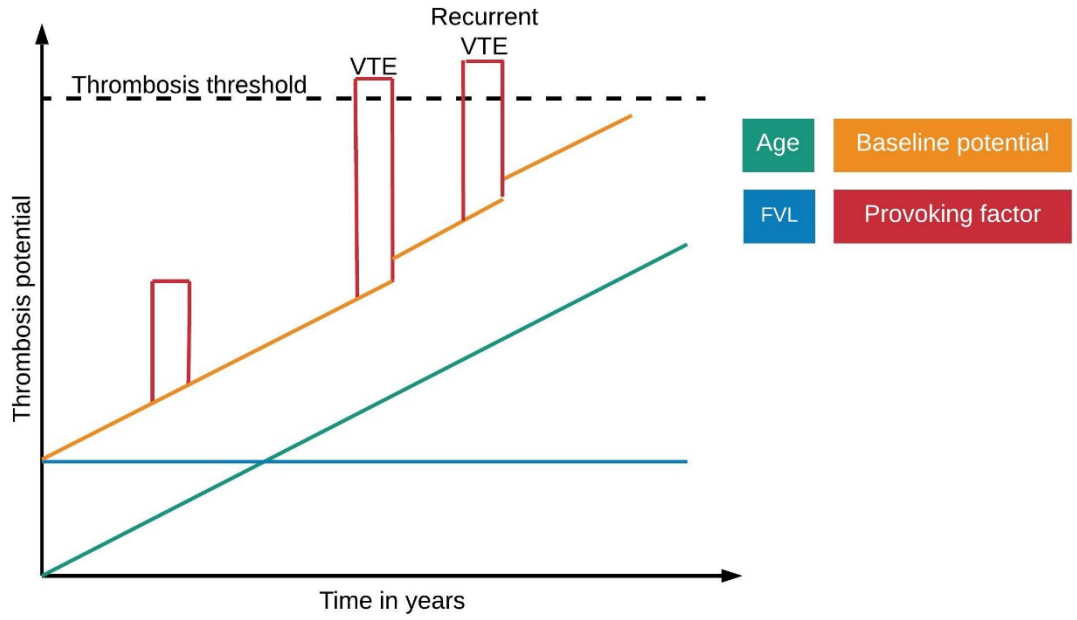

Figure 3 The thrombosis potential model. Factor V Leiden (FVL) exemplifies a hereditary risk factor. Age represents a risk factor that increases with time. The orange line demonstrates the combination of FVL and age. The red bars represent provoking factors. The model shows that a provoking factor early in life may not be enough to reach the thrombosis threshold, whereas a provoking factor later in life may be enough to exceed the threshold resulting in VTE, and even in a recurrent event if a new provoking factor occurs. (Adapted from Rosendaal, Lancet 1999)

1.3.1 Hereditary risk factors

Family and twin studies have shown that the individual susceptibility to VTE harbors a strong hereditary component. This is characterized by a 2 to 3-fold increased risk in first-degree relatives and the overall heritability is estimated to be 45 to 60%.[57-59] The inherited thrombophilias are primarily within in the coagulation or fibrinolytic pathways, and are broadly classified as either loss-of-function or gain-of-function mutations. [52] The former is less common, but has a larger impact on the VTE risk.[52,60]

Antithrombin (AT), Protein C and protein S are main natural inhibitors of the coagulation system, and deficiencies of these represent well-known loss-of-function mechanisms of thrombophilia. **AT** regulates coagulation at several steps (mainly thrombin and FXa), and its function is greatly potentiated by heparin.[52] Although AT deficiency may be caused by numerous different mutations (>250), it is rare in the general population (0.02%) and associated with a 10 to 50-fold increased risk of VTE.[52,61] Activated **Protein C (APC)** inactivates FVa and FVIIIa, and **Protein S** serves as its co-factor.[52,61] Protein S is also a co-factor of tissue factor pathway inhibitor (TFPI) in the inhibition of factor Xa.[52] Numerous different mutations have

been described in patients with these deficiencies, which are rare in the general population (<1%) and associated with an 8 to 10-fold increase in VTE risk.[61,62]

Among the gain-of-function mutations, the **non-O blood group** is the most common with a prevalence of 50 to 60%.[63] The associated thrombophilia is potentially caused by increased levels of vWF and FVIII, but the relationship between non-O blood group and VTE risk remains after adjustment for these factors suggesting additional mechanisms.[61] Compared with the blood group O, blood groups A_1 and B are associated with a 1.5 to 2-fold increased risk of VTE.[37,63] The **FVL mutation** is another well-known cause of thrombophilia, in which the cleavage site for APC on FV is structurally altered leading to APC resistance.[64,65] The FVL mutation is almost exclusively observed among Caucasians in whom the prevalence is approximately 5%.[52,61] Compared with non-carriers, the risk of VTE is increased by 2 to 5-fold in heterozygous carriers and 10 to 80-fold in homozygous carriers of the FVL mutation.[64,66] The **prothrombin G2021A mutation** is associated with increased levels of prothrombin, and hypercoagulability due to enhanced thrombin generation.[67] Like FVL, this mutation is rare outside the Caucasian population, in which the prevalence is 1 to 3%.[66,68] Carriers of the prothrombin G2021A mutation have a 3 to 4-fold increased risk of VTE compared with non-carriers.[61,67]

The introduction of high-throughput micro-array based genotyping technologies in the early 2000s facilitated for hypothesis-free search for susceptibility variants.[60] In addition to confirming previous findings, genome wide association studies (GWAS) have led to the identification of several novel genes/loci associated with VTE risk.[69] However, the majority of these have only a modest influence on VTE risk, and the clinical utility may be limited.[61] To date, 17 genes have been robustly demonstrated to harbour variants associated with VTE risk.[60,70] Although the debate on the extent of missing heritability in VTE is ongoing, future efforts may reveal both common variants with low effect sizes and rare/private mutation with large effect sizes.[69]

1.3.2 Acquired risk factors

Epidemiological studies have identified an extensive list of acquired risk factors for VTE. Some of these are increasing age, obesity, cancer, surgery, hospitalization, and in women, pregnancy and exogenously administered hormones. Whereas some of the acquired risk factors are classified as provoking factors (e.g., surgery, pregnancy, cancer), others (e.g., increasing age) are not.[18]

Increasing **age** is probably the most important risk factor for VTE, and it estimated that 70 to 90% of VTE events in the population can be ascribed to aging.[71,72] The incidence increases exponentially after the age of 50 years, and the risk is almost 80-fold higher in those ≥85 years compared with those aged 20 to 30 years.[9,13,25] Reasons for the profoundly increased risk in the elderly are many, and potentially include degenerative or functional alterations in the vascular system, age-related procoagulant changes in the hemostatic system, or overall frailty and immobility.[41,71,73] A higher comorbid burden among the elderly has also been proposed, although data from the Tromsø Study suggested that a higher incidence of cancer could not explain the increased risk of VTE with advancing age.[74]

Obesity is a well-established causal risk factor for VTE, and the risk increases with BMI in a dose-dependent manner.[75-77] Obesity defined by BMI (BMI ≥30 kg/m^2) is associated with 2 to 3-fold increased risk of VTE compared to normal weight (BMI <25kg/m^2).[75] Other measures of obesity, such as waist circumference, hip circumference and waist-to-hip ratio, are also associated with an elevated VTE risk. However, obesity defined by waist circumference (≥88 cm in women and ≥102 cm in men) has been found to yield the largest effect sizes and identified most individuals at risk among the different anthropometric measures.[75,78] Due to the high prevalence, obesity is an impactful risk factor and it is estimated that more than 30% of unprovoked VTE events can be attributed to a high BMI.[72] In addition to a direct causal effect, potential mechanism for the increased VTE risk with obesity may include procoagulant and hypo-fibrinolytic changes in plasma, chronic low-grade inflammation and impaired venous return due to raised intra-abdominal pressure.[75,79]

Cancer is another important risk factor for VTE, and approximately 20 to 25% of all incident VTE events are cancer-associated.[19,80] Compared with the general population, patients with cancer have 4 to 7-fold higher risk of VTE, and the risk peaks in the period 6 months before to 12 months after the cancer diagnosis.[80,81] Cancers are highly heterogeneous diseases, and the cancer sites most strongly associated with VTE are those of the lungs, brain, pancreas, ovaries, as well as hematological cancers.[80,82] The mechanisms behind the association between cancer and VTE risk probably differ between cancers, but are potentially related to platelet activation, altered synthesis of anticoagulant factors or clearance of procoagulant factors, coagulation activation by tumor-derived TF-positive EVs, or injury from local tumor invasion. Moreover, cancer patients are frequently exposed to conventional risk factors for VTE, such as hospitalization, immobilization and surgery.[83-85]

It is estimated that more than half of all VTE events can be attributed to current or recent **hospitalization** or residency in **nursing homes**, and hospitalized patients have more than 100-fold increased risk of VTE compared with community residents.[86,87] The magnitude of the impact of VTE on the population is illustrated by the fact that hospital-related VTE is among the leading causes of disability-adjusted life-years lost worldwide.[39] The risk is increased both in surgical patients and those with medical illnesses, and may be mediated by the cause of hospitalization (e.g., trauma and acute disease), in-hospital procedures (e.g., surgery and central venous catheters) as well as immobilization. In **major trauma** patients, the absolute risk of VTE was reported to be 50% in the absence of adequate thromboprophylaxis.[88] **Major surgery** is also an important risk factor associated with 4 to 22-fold increased risk, and neurosurgery, total hip arthroplasty and major vascular surgery are identified as particularly high-risk procedures.[89,90] **Acute medical conditions**, such as heart failure, myocardial infraction (MI), ischemic stroke, respiratory disease and infections, are also associated with an increased risk of VTE.[91] **Immobilization** often accompanies acute disease or injury, and is a well-known risk factor for VTE associated with a twofold increased risk in patients presenting at an emergency department.[92] Essentially all circumstances characterized by immobilization (e.g., plaster cast, bed rest, long-haul travel and paralysis) are associated with an increased risk of VTE.[48-51]

Pregnant women have a 4 to 5-fold higher risk of VTE compared with non-pregnant women of the same age, and the risk peaks during postpartum period.[93,94] Although the absolute VTE risk is low (approximately 1.2 per 1000 deliveries), pregnancy-related VTE is a leading cause of maternal morbidity and mortality.[95] Pregnancy is associated with procoagulant changes of the hemostatic system, potentially to minimize the risk of major bleeding during childbirth. Other mechanism for the increased VTE risk in pregnancy and postpartum include increased venous capacitance and stasis.[53,96]

Use of exogenous hormones, including combined oral contraceptives (COC) and postmenopausal hormone therapy (HRT) are established risk factors for VTE. The VTE risk in COC-users is 3 to 4-fold higher compared with non-users, but varies according to the progestogen and the dose of ethinylestradiol in the COC under study.[97] Among women on HRT, the risk of VTE is approximately 2 to 4-fold higher than in non-users. For both COC and HRT, the risk of VTE is highest during the first period (months) of use.[98,99] The VTE risk associated with use of exogenous hormones is mediated by procoagulant changes in the coagulation and fibrinolytic systems.[99]

Several of the established risk factors for VTE are common in the general population, and some induce a more than additive effect on VTE risk under combined exposure (i.e., interaction).[56] E.g., double heterozygosity of FVL and prothrombin G2021A is associated with a 20-fold increase in VTE risk compared with non-carriers, which largely exceed the sum of the individual relative risks.[100] Moreover, both the FVL and the prothrombin G2021A mutations are shown to potentiate the VTE risk associated with COC use, pregnancy and obesity.[94,100-102] Likewise, COC use represents a stronger risk factor in obese compared with normal-weight women.[103]

1.4 Physical activity, cardiorespiratory fitness and health

Physical activity is broadly defined as "*any bodily movement produced by skeletal muscles that results in energy expenditure*".[104] Physical activity as a behavior can be described according to dimensions: mode (i.e., the specific activity performed), frequency, intensity and duration, as well as domain (occupational, domestic, transport or leisure). Most often, simply the total amount of time (e.g., per week) at a specific intensity range (e.g., moderate and vigorous) is measured.[105]

The significance of physical activity for health was valued already 2000 years ago by the classical Greek physicians Herodicus, Hippocrates and Galen.[7] Later, the implementation of modern statistics and epidemiological methods facilitated for quantification of the association, and seminal work by Professor Jeremy Morris and colleagues in the 1950s defined the genesis of physical activity epidemiology.[7,106] Through a series of studies, they demonstrated an inverse association between occupational physical activity and the risk of coronary heart disease, and found that active individuals tended to develop less severe disease that also occurred at an older age.[7,106] This work was followed by numerous investigations, and today there is overwhelming evidence on the benefits of physical activity. Perhaps the most comprehensive review of the literature so far was recently conducted by the US 2018 Physical Activity Guidelines Advisory Committee, which culminated into a Scientific Report summarizing the existing evidence on physical activity and health.[4] Physical activity is convincingly associated with many of the most common diseases. The list of benefits includes, but is not limited to, lower risk of premature all-cause mortality, cardiometabolic conditions (e.g., heart disease, stroke and type-2 diabetes), several cancers, as well as improved brain health. The dose-response relationship between moderate- to vigorous physical activity and

selected outcomes are shown in Figure 4.[107] It shows that there is no lower limit of activity for achieving health benefits, that the largest benefits are harvested at the low end of the activity spectrum, and that the slope of the curve diminished at very high levels of weekly physical activity.[107]

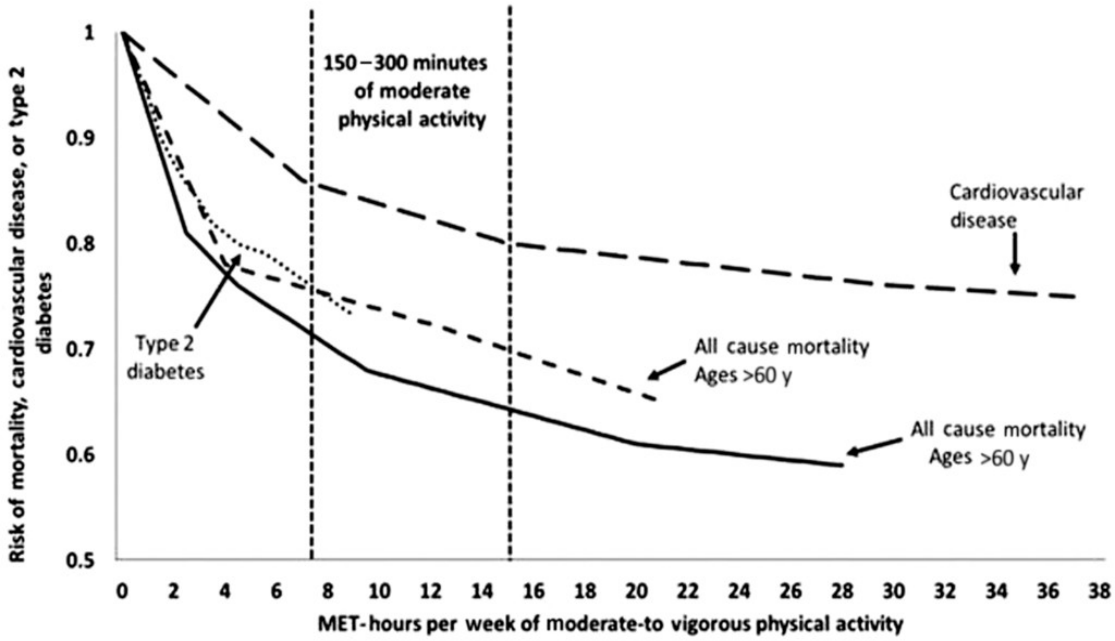

Figure 4 The association between moderate- to vigorous physical activity and the risk of all-cause mortality, cardiovascular disease and type-2 diabetes.

Reprinted by permission from K.E. Powell, A.C. King, D.M. Bucher, et al., "The Scientific Foundation for the Physical Activity Guidelines for Americans, 2nd Edition," *Journal of Physical Activity and Health* 16, no. 1 (2019): 1-11, https://doi.org/10.1123/jpah.2018-0618. © Human Kinetics, Inc.

The current guidelines for physical activity for health benefits in adults are relatively harmonized worldwide, and recommends that all adults should accumulate at least 150 minutes per week of moderate intensity, or 75 minutes per week of vigorous intensity activity, or an equivalent combination of these. Additional benefits can be achieved with physical activity up to twice the minimum amount. Muscle-strengthening activities are recommended twice per week, and it is generally advised to move more and sit less throughout the day.[108-111] Although the majority of the current literature relates to the benefits of physical activity of moderate- and vigorous intensity, emerging evidence support considerable health benefits associated with light intensity activity.[112,113]

Physical activity (or its absence) influences physical fitness. While there are several different components of fitness (i.e., muscle strength, flexibility etc.), we here focus on the cardiorespiratory component.[104] Cardiorespiratory fitness (CRF) is defined as the capacity of

the respiratory, circulatory and muscular systems to supply and consume oxygen during sustained physical activity.[104,114] The relationship between physical activity and CRF has been demonstrated to both extremes in bed rest studies and exercise trials.[115-117] However the individual variation in CRF is also determined by age, sex, genes, comorbidity, as well as body size and composition.[114,118] The relationship between CRF and health outcomes was not described until the 1980s, however, following the influential study by Blair and colleagues in 1989 demonstrating a strong inverse association between CRF and mortality, the evidence has accumulated.[119,120] In addition to lower risk of premature mortality, the benefits of a higher CRF includes lower risk of incident arterial CVD, some cancers, type-2 diabetes and dementia [117,121-124] Importantly, CRF appears to be more strongly associated with health outcomes compared with physical activity.[125-127] The comprehensive evidence and impressive predictive abilities of CRF prompted a Scientific Statement by the American Heart Association in 2016 advocating for the implementation of CRF as a clinical vital sign.[117] However, routine assessment of CRF in clinical practice still awaits partly due to the lack of established reference values.[120,128]

1.5 Physical activity, cardiorespiratory fitness and venous thromboembolism

Physical activity has profound impact on organ systems throughout the body, and the field of exercise biology has made important contributions to our mechanistic understanding of the benefits of physical activity.[129,130] This includes pathways related to the pathophysiology of VTE. During activity, an increase in blood flow is apparent[114], and this is potentially accompanied by an antithrombotic flow profile.[131,132] Longer term adaptations include improved endothelial function[133,134], and beneficial changes in hemorheological properties are also suggested.[135] In addition, transient responses to acute activity are observed in both the hemostatic and fibrinolytic systems. However, it is unclear whether these responses result in a net hypercoagulable state, and this may depend on the age and training status of the individual.[136-139] In contrast, the available data suggest that the long-term responses in the hemostatic and fibrinolytic systems during rest probably are moderate.[140-142]

While the role of physical activity in relation to the risk of arterial CVD is long established, the first report on physical activity and VTE was published in 2002 when Tsai and colleagues investigated established risk factors for arterial CVD, in relation to VTE.[143] Analyzing data from the Longitudinal Investigation of Thromboembolism Etiology (LITE), they did not observe an association between physical activity and the risk of incident VTE.[143]

Later, several studies have addressed the association between physical activity and incident VTE, and conflicting results have been reported (Table 1). In total, data from five prospective studies suggest that physical activity is associated with a lower risk of incident VTE. In the Atherosclerosis Risk in Communities (ARIC) study, higher scores on the Baecke sports questionnaire were associated with 19 to 31% lower risk of VTE.[144] Likewise, in the Million Women study, engagement in physical activity on a weekly basis was associated with 4 to 34% lower risk of VTE. Two studies have reported on the physical activity component of the American Heart Association's Life's Simple 7 metric. In both the Reasons for Geographical and Racial Differences in Stroke Study (REGARDS) and the Multi-Ethnic Study of Atherosclerosis (MESA), a higher amount of physical activity was associated with 30 to 41% lower risk of incident VTE.[145,146] Additionally, in the Iowa Women's Health Study (IWHS), a higher frequency of moderate and vigorous physical activity was associated with 9 to 19% lower risk of VTE, but the association was non-significant after adjustment for BMI.[147] Kim and colleagues used data from the Nurses' Health Study (NHS; I and II) and the Health Professionals Follow-up Study (HPFS) to establish a nested case-control study (primary aim was study interactions between a genetic risk score and environmental risk factors).[148] They reported that a higher amount of weekly physical activity was associated with 15 to 30% lower risk in NHS I, a non-significant 8 to 20% lower risk in NHS II, and 31 to 34% lower risk in HPFS. There was no evidence of interaction between the genetic risk score and physical activity.[148] Moreover, in two case-control studies[149,150], and in a cohort study with retrospective exposure assessment[151], physical activity was associated with a lower risk of incident VTE. In the abovementioned studies, it appeared that the largest benefit occurs between the least active and the second least active category (i.e., in the low end of the activity spectrum), and with the exception of the REGARDS Study[146], there is limited evidence of a dose-dependent relationship.

On the contrary, although a beneficial association between weekly participation in physical activity and VTE risk was reported in the Million Women study, they observed an 8% (non-significant) increased VTE risk in women who did strenuous activity on daily basis when compared with those who were inactive.[8] A similar pattern was observed in the Cardiovascular Health Study (CHS), where strenuous physical activity was associated with 75% higher VTE risk compared with no activity, whereas low-intensity activity was associated with a non-significant lower risk of VTE.[152] Further, a 9% increase in VTE risk per exercise category was reported in the Physicians' Health Study.[2] Finally, similar to the mentioned LITE-report, some

studies did not observe any association between physical activity and the risk of VTE. This includes, the Tromsø study[153], Copenhagen City Heart study[154] and the NHS I (PE only)[155], where various measures of physical activity were not found to be significantly associated with the risk of VTE. In summary, the association between physical activity and VTE risk has been extensively studied, but the existing results are conflicting. The discrepancy may relate to differences in methodology, such as study design and populations, assessment of physical activity and data analysis (e.g., handling of modifiable risk factors and choice of confounders). In order to advance our knowledge, there is a need for a thorough summary of the existing data and identification of focal points for future research.

The association between objectively assessed physical activity, such as accelerometer measurements, and VTE risk remains to be explored. Similarly, measures of physical fitness, such as CRF and muscle strength, has received limited attention as potential risk factors for VTE. Thus far, the association between CRF and the risk of incident VTE has been addressed in two studies. In a Swedish study of male conscripts (18 to 20 years), Zöller and colleagues found that one standard deviation (SD) increase in CRF was associated with 19 to 24% lower risk of unprovoked incident VTE.[156] The association between CRF and VTE was also addressed in a Finnish cohort of men aged 42 to 61 years, The Kuopio Ischaemic Heart Disease Risk Factors Study (KIHD), where higher CRF was associated with a non-significant 18 to 20% lower risk of incident VTE.[157] An important limitation of the Swedish study was that more than 80% of the VTE events occurred in individuals younger than 50 years (mean age at VTE was 42 years), which is markedly lower than the mean age at incident VTE in the general population (~70 years).[9,156,158] Further, the association between CRF and VTE risk in women and in a general population of a wider age-range remains to be investigated.

Whether physical activity or CRF may modify the risk of complications, such as recurrence and mortality, after incident VTE is largely unknown. Flintermann and colleagues[159] investigated the association between a sedentary lifestyle and recurrence risk in a follow-up arm of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. While no association was observed in men, women who were largely sedentary at the time of incident VTE had a 1.5-fold higher recurrence risk compared with women who were more active.[159] However, no study has addressed the association between physical *activity* and the risk of VTE recurrence. In relation to mortality, a Swiss study (SWITCO65+) of VTE patients aged 65 years and older found that a low activity level reported at the time of the event was associated with an almost twofold higher risk of mortality during 3

years of follow-up.[160] To summarize, data on physical activity in relation to secondary prevention of VTE and mortality risk in patients with VTE are limited. Research is needed to elucidate the necessity of structured rehabilitation and a potential role of physical activity in the management of patients with VTE.

Table 1 Overview of prospective studies on the association between physical activity and VTE

1st author (year)	Cohort	Study population	Follow-up	VTE events	Main findings
Beneficial association					
Armstrong (2015)[8]	Million Women Study	W, 50-64 years	9 years	14,550	4-34% lower risk
Lutsey (2010)[147]	Iowa Women's Health Study (IWHS)	W, 55-69 years	13 years	2,137	9-19% lower risk*
Ogunmoroti (2016)[145]	The Multi-Ethnic Study of Atherosclerosis (MESA)	M+W, 45-86 years	10 years	215	30-34% lower risk
Olson (2015)[146]	The Reasons for Geographical and Racial Differences in Stroke (REGARDS) Study	M+W, 45 years and older	5 years	263	30-41% lower risk
Wattanakit (2012)[144]	The Atherosclerosis Risk in Communities (ARIC) Study	M+W, 45-64 years	16 years	468	19-31% lower risk
Adverse association					
Armstrong (2015)[8]	Million Women Study	W, 50-64 years	9 years	14,550	8% higher risk
Glynn (2005)[2]	Physicians' Health Study	M, 40-84 years	20 years	358	9% higher risk
Van Stralen (2008)[152]	The Cardiovascular Health Study (CHS)	M+W, 65 years and older	12 years	171	75% higher risk
No association					
Borch (2010)[153]	The Tromsø Study	M+W, 25-97 years	13 years	460	No association
Holst (2010)[154]	Copenhagen City Heart Study	M+W, 20 years and older	20 years	969	No association
Kabrhel (2011)[155]	Nurses' Health Study (NHS)	W, 30-55 years	18 years	268 (PE)	No association
Tsai (2002)[143]	The Longitudinal Investigation of Thromboembolism Etiology (LITE: ARIC and CHS)	M+W, 45 and older	8 years	215	No association

M, men; W, women.

*Not significant after adjustment for BMI

2 Aims of the thesis

The aims of the thesis were:

- To summarize the epidemiological evidence on the association between physical activity and risk of VTE and VTE related complications, address methodological challenges in this context and put forward plausible biological mechanisms (Paper I)

- To investigate whether physical activity was associated with the risk of incident VTE in a population-based cohort with repeated assessment of physical activity, and to explore the role of BMI as a mediator of an association (Paper II)

- To investigate the association between estimated CRF (eCRF) and the risk of incident VTE in a population-based cohort, and to study whether an association was influenced by body weight status (Paper III)

- To investigate the association between physical activity and the risk of recurrent VTE and all-cause mortality in a cohort of patients recruited from the general population (Paper IV)

3 Methods

3.1 Study population

The papers in the thesis are based on data from the Tromsø Study, a single-center population-based study with repeated health surveys of the inhabitants of Tromsø municipality in Norway. The study was initiated in 1974 with the aim to reduce the high mortality from cardiovascular diseases in the northern part of Norway. The scope of the study has expanded over the years and now includes a broad spectrum of somatic and psychiatric diseases. To date (2019), seven surveys have been conducted and more than 45,000 unique individuals have participated.[161-163]

Paper I is primarily a narrative review of the already published literature, but is substantiated with analyses based on data from the fourth survey of the Tromsø Study that was conducted in 1994-95. In Tromsø 4 the entire population aged ≥25 years (age-range 25 to 97 years) was invited and 27,158 participated (77% of the eligible). For the analyses in Paper I, participants with data on physical activity were followed from inclusion to incident VTE, migration, death or study end (December 31, 2013) in one analysis, and to incident MI, migration, death or study end in a separate analysis. As the association between physical activity and the risk of MI is well established, this approach was used as an example to illustrate indirect validation of the exposure variable (physical activity).

Paper II is based on data from Tromsø 4 to 6. Tromsø 5 and 6 were conducted in 2001-02 and 2007-08, respectively. Total or samples of total birth cohorts were invited, and 8,130 (79% of the eligible) participated in Tromsø 5 and 12,984 (66% of the eligible) participated in Tromsø 6. The age-range of the participants was 30 to 89 years and 30 to 87 years in Tromsø 5 and 6, respectively. For the purpose of Paper II, participants with data on physical activity were followed from inclusion to the date of incident VTE, migration, death or to the end of the observation period. The observation periods ended on the date of the next possible survey for periods starting at Tromsø 4 and 5, and on December 31, 2016 for Tromsø 6 (Figure 5). Those who attended multiple surveys had their exposure data updated at each time point, and contributed with observation periods corresponding to the number of partaken surveys. Paper III is based on data from Tromsø 6, and participants with data necessary for estimation of CRF were followed from inclusion to incident VTE, migration, death or December 31, 2016.

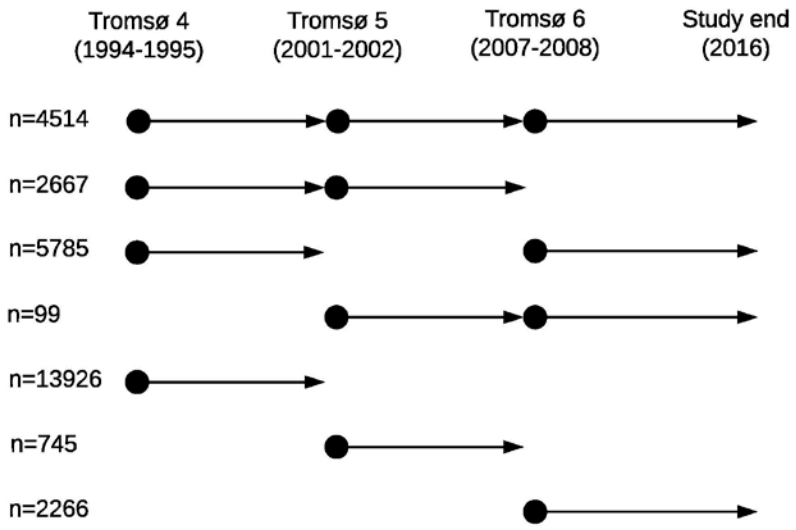

Figure 5 Overview of study participation (dots) and observation periods (arrows) in Paper II.

The source population in Paper IV is participants in Tromsø 4 to 6, and the study population comprises of individuals who developed incident VTE in the time period from study inclusion to December 31, 2015. Those with data on physical activity in the last survey they participated in prior to the incident VTE event were followed from the date of the event to a recurrent event, death, migration or December 31, 2015. For the analyses on mortality, recurrence and migration were not included as censoring event.

3.2 Exposure assessment

Participant information was obtained from 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 ($kg \cdot m^{-1}$). Waist circumference was measured in centimeters at the umbilical line. Blood pressure was recorded using an automatic device (Dinamap Vital Signs Monitor 1846; Criticon, Tampa, FL) after 2 minutes of rest in a sitting position. Three readings were made with 2-minute intervals, and the mean of the two latter was used in the analyses. Resting heart rate was recorded during the blood pressure recordings, and the mean of readings two and three were used for analysis. Non-fasting blood samples were collected from an antecubital

vein. Serum was prepared by centrifugation after 1 hour (h) of respite at room temperature and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway (UNN), Tromsø, Norway.

Information on current smoking (yes/no), higher education (≥15 years: yes/no) and history of CVD (i.e., MI, ischemic stroke or angina pectoris) was obtained via self-administered questionnaires. Data on history of cancer was obtained from the Cancer Registry of Norway, and data on cancer in relation to VTE was obtained through review of the patients' medical records.

3.2.1 Physical activity

Information on habitual physical activity was obtained from self-administered questionnaires. In Tromsø 4 and 5, the 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 the past year according to four categories (none, <1h, 1-2h or ≥3 h). The reliability and validity of the physical activity questionnaire used in Tromsø 4 and 5 were investigated in 108 men aged 20 to 39 years.[164] Reliability was evaluated in a test-retest design where the questionnaire was administered twice separated by one week, and the validity was assessed by comparing responses from the questionnaire with data from motion sensors, CRF assessed as maximal oxygen uptake (VO_{2max}) and the International Physical Activity Questionnaire (IPAQ). It was found that the question on light physical activity had poor reliability (r = 0.17), while the question on hard physical activity had moderate reliability (r = 0.50). Hard physical activity was moderately well correlated (r = 0.31-0.48) with CRF, IPAQ and time spent in vigorous activity assessed by motion sensors, whereas light physical activity was less well correlated with the comparison measures.[164]

A different question for assessment of physical activity was administered to the participants in Tromsø 6. Here, the questions related to weekly frequency (never, less than once, once, 2 to 3 times or approximately every day), duration per session (<15 min, 15-29 min, 30-60 min or >1 hour, and intensity (not short-winded or sweaty, becoming short-winded or sweaty or becoming exhausted). The reliability and validity of the questionnaire have been evaluated similarly as the questionnaire in Tromsø 4 and 5.[165] The reliability for the three questions was reported to be good (r = 0.76-0.87). The individual questions and a summary index based on all three questions correlated well with the other measures of physical activity, particularly with vigorous activity, and with CRF.[165] To obtain compatibility with the questionnaire used in Tromsø 4 and 5, the total weekly duration of physical activity was calculated as the sum of

weekly duration and average duration per session. Further, the lowest intensity-category was considered equal to light physical activity and the two highest intensity-categories equal to hard physical activity in Tromsø 4 and 5. In those with missing information on intensity, low intensity was recorded.

A five-level variable of physical activity was constructed where the inactive category comprised of those reporting 'no activity' or <1 h per week', and the four active categories comprised of: '1-3 h per week of light activity', >3 h per week of light activity, 1-3 h per week of hard activity' and >3 h of hard activity' (Table 2). A dichotomous variable was made by merging the four activity categories while the inactive category was kept unchanged.

		Light physical activity (per week)*			
Hard physical activity (per week)†		No	<1h	1-2h	≥3h
	No	1	1	2	3
	<1h	1	1	2	3
	1-2h	4	4	4	4
	≥3h	5	5	5	5

Table 2 Matrix of the categorization of physical activity.

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

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

3.2.2 Cardiorespiratory fitness

In Paper III, CRF was estimated from a non-exercise algorithm developed from 4,637 healthy participants aged 20 to 90 years in the Nord-Trøndelag Health Study (HUNT).[166,167] The algorithm was sex-specific and based on age, waist circumference, resting heart rate and a physical activity index. The physical activity index was calculated by multiplying weighted values from responses on the physical activity questions in Tromsø 6. The algorithms for estimated CRF (eCRF) were[166]:

***Women**: 74.74 - (0.247 × age) – (0.259 × waist circumference) - (0.114 × resting heart rate + (0.198 × physical activity index)*

***Men**: 100.27 - (0.296 × age) – (0.369 × waist circumference - (0.155 × resting heart rate) + (0.226 × physical activity index)*

The gold standard for assessing CRF is through direct measurement of oxygen uptake during a maximal exercise test.[168] eCRF assessed from the algorithm was reported to explain 61% and 56% of the variance in directly measured CRF in men and women, respectively. The accuracy, assessed by standard error of the estimate, was 12.8 % in men and 14.3% in women. Cross-validation, assessed by data splitting procedures, revealed good stability of the model, and indicated that it may be generalized to similar populations without major loss of accuracy. It was, however, noted that CRF tended to be overestimated in the low fit and underestimated in highly fit individuals.[166] eCRF derived from the algorithm has been shown to predict CVD and all-cause mortality.[169]

For the analyses in Paper III, participants were categorized according to age- (by ten years) and sex-specific categories: low eCRF (quintile 1), moderate eCRF (quintiles 2+3) and high eCRF (quintiles 4+5). eCRF was also expressed as metabolic equivalents (METs; 1 MET is approximately 3.5 mL $\cdot$ kg^{-1} $\cdot$ min^{-1}) and as a fraction of age-predicted CRF (women: 55.6 - 0.328 x age, men: 63.6 - (0.393 x age).[117,169]

3.3 Outcome assessment

All VTE events during follow-up were identified by searching the hospital discharge registry (outpatients and hospitalizations), the autopsy registry and the radiology procedure registry at the UNN. This is the only hospital in the study region, and all relevant diagnostic radiology and care is exclusively provided by this hospital. The relevant discharge codes were International Classification of Diseases (ICD) 9th Revision codes 325, 415.1, 451, 452, 453, 671.3, 671.4, and 671.9 for 1994 to 1998 and ICD 10th Revision, 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 1999 to 2016. Trained personnel who were blinded for baseline variables reviewed the medical record for each potential VTE case. The adjudication criteria for potential VTE cases were: (i) signs and symptoms of DVT or PE, (ii) objective confirmation by a diagnostic procedure (i.e., compression ultrasound, venography, spiral computed tomography, ventilation-perfusion scan, pulmonary angiography or autopsy, (iii) the medical record indicated that a DVT or PE diagnosis was made by a physician, and (iv) the patient was treated with anticoagulants (heparin, warfarin or direct oral anticoagulation), thrombolytic therapy or vascular surgery (unless contraindications were specified). All four criteria were required for recording a case. Potential cases identified through the autopsy registry were only recorded if VTE was described

as the cause of death or a significant contributor to death in the autopsy report. Recurrent VTE events were identified and adjudicated similarly as the incident events.

All VTE events were classified according to clinical presentation (i.e., as DVT or PE with or without DVT), and according to the presence of provoking factors at the time of the event. Factors defining a provoked event were: surgery or trauma (within 8 weeks prior to the event), acute medical conditions (acute MI, ischemic stroke, or major infectious disease), active cancer, immobilization (bedrest ≥3 days, confined to wheelchair or long-distance travel ≥4 h within the previous 14 days), or another provoking factor (e.g., intravascular catheter) described by a physician in the medical record. Cancer was recorded as a provoking factor if VTE occurred in a patient with overt cancer or if cancer was diagnosed within one year after the VTE event. If no provoking factor was present, the events were classified as unprovoked.

3.4 Ethics

The present thesis is a part of a larger project run by K.G. Jebsen TREC, which has been approved by the Regional Committee for Medical and Health Research Ethics. All participants in the Tromsø study provided written informed consent prior to inclusion, and are free to withdraw their consent at any time.

4 Main results

4.1 Paper I

Regular physical activity and risk of venous thromboembolism

Studies on physical activity and the risk of incident VTE have reported conflicting results, and limited data exist on the role of physical activity in the prevention and treatment of VTE related complications. Moreover, methodological matters may influence the findings and interpretation of the studies in this context. The focus of the present review was to summarize the existing epidemiological evidence on the association between physical activity and risk of VTE and associated complications, to discuss methodological challenges in this context and to put forward plausible biological mechanisms. The PubMed database was searched for relevant publications by using combinations of the terms ‘physical activity’, ‘physical inactivity’, ‘venous thromboembolism’, ‘deep vein thrombosis’ and ‘pulmonary embolism’. Relevant publications were also identified through PubMed links and by cross-referencing from the reference lists of the retrieved papers.

Despite a complex picture, we argued that the available evidence was balanced towards a small beneficial effect of physical activity on the risk of incident VTE, but not in a dose-dependent manner. There are several plausible biological mechanisms in support of a favorable association between physical activity and lower risk of thrombosis, and these relate to all aspects of Virchow’s triad. Importantly, the field is characterized by the lack of an operational definition and standardized assessment methods of physical activity. It is also unclear whether weight status ought to be treated as a confounder or a mediator in this context, and there is a need to address potential regression dilution bias in studies with long follow-up.

We conclude that future studies are needed. These should utilize objective assessment strategies of physical activity and cardiorespiratory fitness, account for the fluctuating nature of physical activity, and explore the role of physical activity in areas of secondary prevention and VTE related complications.

4.2 Paper II

Repeated assessments of physical activity and risk of incident venous thromboembolism

It is unclear whether physical activity influences the risk of incident VTE. The aim of this study was to investigate the association between physical activity and VTE risk using repeated assessments of physical activity to account for changes in activity habits over time, and to evaluate the role of BMI as a mediator of the potential association. Participants (n=30,003) attending one or more surveys of the Tromsø Study 4 to 6 (1994-95, 2001-02, and 2007-08) who provided data on physical activity were included. Incident VTE was recorded from enrolment to December 31, 2016. Participants attending multiple surveys had their exposure data updated, and contributed with several observation periods. Time-varying Cox regression models were used to estimate hazard ratios (HRs) across categories of physical activity. The Aalen additive hazard model was used to quantify the total, direct and indirect (mediated by BMI) effect of physical activity on VTE risk.

Mean duration per observation period was 6.8 years, and there were 531 incident VTE events. Compared with inactive (physical activity <1 h per week), active individuals (physical activity ≥ 1 h per week) had 23% lower risk of VTE (HR 0.77, 95% confidence interval [CI] 0.64-0.92) in the age- and sex-adjusted model. The association was strongest among those aged ≥65 years (HR 0.70, 95% CI 0.55-0.88) and in relation to provoked VTE (HR 0.66, 95% CI 0.50-0.89), whereas no significant association was observed in those aged <65 years (HR 0.85, 95% CI 0.64-1.13). Adjustment for BMI attenuated the risk estimates by 7-12%, whereas further adjustment for history of CVD and cancer did not alter the risk estimates. The absolute risk differences between active and inactive individuals were -0.42 (95% CI -0.73 to -0.14) and -1.59 (95% CI -2.74 to -0.52) events annually per 1000 individuals in the total population and those aged ≥65 years, respectively. BMI mediated 14-36% of the association between physical activity and VTE risk. When the association was explored across five levels of physical activity, there was no evidence of a dose-dependent relationship.

In conclusion, our findings suggest that regular physical activity is associated with a lower risk of VTE, particularly in those aged ≥65 years and in relation to provoked events. The association occurred at a relatively low level of physical activity, with no evidence of a dose-dependent relationship. A moderate proportion of the association was mediated by BMI, and the association was independent of CVD and cancer.

4.3 Paper III

Cardiorespiratory fitness and future risk of venous thromboembolism

CRF is a robust health indicator, but it is unknown whether it influences the risk of incident VTE. The aim of this study was to investigate whether estimated CRF was associated with the risk of incident VTE, and to evaluate the impact of weight status on a potential association. A total of 10,393 individuals participating in Tromsø 6 (2007-08) were included, and incident VTE was recorded to December 31, 2016. eCRF was estimated using sex-specific algorithms based on age, waist circumference, resting heart rate and self-reported physical activity. Participants were categorized according to age-predicted eCRF (<85%, 85-100% and >100%) and age- and sex-specific percentiles of eCRF: low (<20^{th} percentile), moderate (20^{th}-60^{th} percentile) and high (>60^{th} percentile). The impact of weight status was investigated in stratified analyses (normal weight: BMI<25 kg·m^{-2}, overweight/obese: BMI ≥25 kg·m^{-2}).

There were 176 incident VTE events during a median of follow-up of 8.1 years. Compared with individuals with CRF <85% of age-predicted, those with eCRF of 85-100% and >100% of age predicted had 46% (HR 0.54, 95% CI 0.39-0.74) and 67% (HR 0.33, 95% CI 0.20-0.54) lower VTE risk, respectively. The association between age-predicted eCRF and VTE risk was of similar magnitude across subgroups of VTE stratified by clinical presentation and presence of provoking factors. Compared with overweight/obese individuals with eCRF <85% of age-predicted, overweight/obese individuals with eCRF ≥85% of age-predicted had 50% (HR 0.50, 95% CI 0.35-0.74) lower VTE risk and normal weight individuals with eCRF ≥85% of age-predicted had 55% (HR 0.45, 95 CI 0.30-0.68) lower risk. The risk of VTE in normal weight individuals with eCRF <85% of age-predicted were similar as the risk in overweight/obese with eCRF <85% of age-predicted (HR 1.06, 95% CI 0.57-1.97). When the association between eCRF and VTE risk was explored across age- and sex-specific categories, participants with moderate and high eCRF had 37% (HR 0.63, 95% CI 0.44-0.90) and 54% (HR 0.46, 95% CI 0.32-0.68) lower risk of VTE, respectively, compared with those with low eCRF.

To conclude, our findings suggest that eCRF estimated from easily available variables is associated with a lower risk of incident VTE. This association was independent of weight status and implies that higher eCRF may modify the VTE-risk associated with overweight and obesity.

4.4 Paper IV

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

Studies suggest that physical activity is associated with a lower risk of incident VTE, but limited data exist on the relationship between physical activity and major complications after VTE. Therefore, this study aimed to investigate whether physical activity was associated with the risk of recurrence and mortality in patients with incident VTE. Patients with incident VTE (n=786) derived from participants in Tromsø 4-6 (1994-95, 2001-02, and 2007-08) were included, and categorized as inactive (physical activity <1 h per week) or active (physical activity ≥ 1 h per week) based on data from the survey prior to the first event. Recurrent VTE and all-cause mortality were recorded from the date of incident VTE to December 31, 2015. HRs for recurrence and all-cause mortality were estimated in Cox regression models. To account for death as a competing event, sub-distribution hazard ratios (SHRs) were estimated according to the method by Fine and Gray.

During a median follow-up of 4.1 years, there were 395 deaths. Compared with inactive, the mortality risk among the active was 19% (HR 0.81, 95% CI 0.57-1.17), 25% (HR 0.74, 95% CI 0.57-0.97) and 28% (HR 0.72, 95% CI 0.57-0.91) lower at 1, 5 and 10 years, respectively, after adjustment for age, sex, smoking, education, history of cardiovascular disease and cancer-related VTE. The association (at 10 years of follow-up) was stronger in patients with an incident DVT (HR 0.59, 95% CI 0.44-0.79) than in patients with a PE (HR 0.87, 95% CI 0.61-1.26).

There were 139 recurrences during a median follow-up of 2.9 years. After ten years of follow-up, there was no association between physical activity and risk of recurrence in women (HR 0.95, 95% CI 0.52-1.74) or in men (HR 1.48, 95% CI 0.83-2.65). Likewise, no associations were observed in subgroups of VTE stratified by clinical presentation and according to the presence of provoking factors. The SHRs were somewhat higher than the HRs, reflecting the difference in mortality between active and inactive individuals.

In conclusion, our findings imply that physical activity prior to incident VTE is not associated with the risk of recurrence. However, active individuals have a lower risk of mortality following VTE, particularly DVT.

5 General discussion

5.1 Methodological considerations

5.1.1 Study design

Epidemiology is both a science and a tool with the intent to understand the causes of disease, quantify the burden of disease, prevent and control disease, and to guide policy and planning of health care. The five core epidemiological study designs are: trial, cohort, case-control, cross-sectional and case series.[170] With the exception of Paper I, the papers in the present thesis are based on data from a population-based prospective cohort, the Tromsø Study. In a cohort study, a defined group of individuals (the cohort) is followed from inclusion until the development of the outcome of interest (e.g., VTE) or the occurrence of another censoring event (e.g., death, migration or study end). The study participants are classified on basis of exposure information (e.g., physical activity level), which subsequently can be related to the occurrence of an outcome. Important strengths of this study design include the possibility to study multiple exposures and outcomes simultaneously, to estimate absolute and relative risks, unbiased exposure information and the clear temporal sequence between exposure and outcome.[170] The latter is imperative but not sufficient for causal inference.[171] In addition, large population-based cohorts, such as the Tromsø Study, are likely to have high external validity and allow for generalization of study findings. Nevertheless, cohort studies also have some shortcomings. These include the considerable demand for time and resources, the potential for loss to follow-up, and it is an inefficient design for studying rare or latent outcomes. Cohort studies are also susceptible to bias and confounding owing to the observational design, as well as the potential for change in exposure status during follow-up. Misclassification due to change in exposure status can, however, be addressed with the use of repeated measurements and time-varying analysis (as discussed in chapter 5.1.4).

Another frequently used design in epidemiology is the case-control study. Compared with the cohort study, this design is more suitable to investigate rare outcomes as it is based on cases and matched control subjects. Moreover, as information on exposure and outcome are collected at the same time, the design is time- and cost-efficient.[170] In addition to the lack of incidence rates, disadvantages in the case-control design mainly relates to the sampling of controls and collection of exposure information. Robust strategies for the selection of control subjects are important to avoid bias, and controls should be representative of the population from which the cases were drawn.[170] Further, the retrospective collection of exposure information is an important constraint of case-control studies. This not only hampers causal inference due to the

lack of a temporal sequence, but also carries a risk of reverse causality and recall bias. Reverse causality occurs when the exposure is determined by the outcome, and can be exemplified in case-control studies on acute phase proteins (e.g., C-reactive protein) and VTE risk, where an association is likely to solely reflect an inflammatory profile caused by the thrombotic event. Recall bias occurs when the cases and controls recall and report exposure differently.[172] In Paper I, recall bias was discussed in the context of physical activity and the risk of VTE. A striking observation in the literature was that all studies that collected exposure information retrospectively reported that a higher amount of physical activity was associated with a lower risk of VTE[149-151], whereas data from prospective studies were less consistent.[2,8,153] As individuals with acute VTE may recall their physical activity habits differently compared with healthy individuals, it is likely that studies with a retrospective assessment strategy are hampered by recall bias.

Experimental evidence is the strongest argument for causation, and the randomized controlled trial (RCT) is the gold standard design for establishing a causal relationship.[171] In an RCT, the participants are randomly allocated to groups (intervention or control), and manipulation of the exposure allows for evaluation of the effect on the outcome. The randomization procedure ensures that all covariates other than the exposure are randomly allocated between groups, and thereby minimizes confounding.[173] Despite the many advantages of RCTs including their high internal validity, strict inclusion criteria may reduce their external validity. Further, RCTs are time- and resource-demanding and may not always be feasible or ethically acceptable. Thus, in many contexts observational studies are a better option.

Advances in genomics have facilitated for the development of a refined form of natural experiments – Mendelian randomization studies, which are now important contributors to epidemiology.[170] This approach uses genetic variants, usually identified through GWAS, as instrumental variables to test potentially causal relationships between a modifiable exposure variable and an outcome. The random segregation of alleles during meiosis underpins the concept and is regarded as analogous to the randomization procedure in RCTs. In this study design, bias from confounding is greatly reduced and reverse causation is eliminated.[174] Important assumptions of the approach are that the genetic instrument must be reliably associated with the exposure under study (the risk factor), and only have an effect on the outcome through this risk factor. Further, the genetic variant must be independent of the outcome through other mechanisms (e.g., other genes, phenotypes).[170,174] Limitations of Mendelian randomization studies are the need for a large sample size, potential linkage

disequilibrium between genetic variants used as instruments, population stratification, weak instruments and pleiotropy of instruments.[174]

5.1.2 External validity

External validity refers to the generalizability of study findings outside the context of the study, i.e., to a different population, setting or time.[175] Although the scientific value of a study in some situations rests on its generalizability, this is only relevant when a high internal validity has been established.[170,176] In addition to internal validity, important determinants of generalizability includes the distribution of exposure and confounders, definition and classification of study variables and the representativeness of the study population.[177]

The Tromsø Study is a population-based study designed to comprise a representative sample of the adult population in the municipality of Tromsø.[162] In the fourth through sixth surveys, complete or representative samples of birth cohorts were invited to participate, and the attendance rates were relatively high (66 to 79%). Pertinent cohort studies for comparison, such as the HUNT study, reported 54 to 89% attendance, and the Danish Cancer and Health (DCH) study reported 35% attendance.[178,179] Nevertheless, a substantial amount (21 to 34%) of those invited did not participate. Commonly, non-attendees in health surveys differ from those who attend in terms of having lower socioeconomic status and higher mortality rates.[180] In the Tromsø Study, subgroups with markedly lower attendance rates were young men, singles, and the very old[162], and generalization of study findings to these groups must therefore be done with caution. In the context of physical activity and the risk of VTE (Paper II), a low attendance rate among those with a presumably high activity level and low VTE risk (i.e., young men) and those with a low activity level and high VTE risk (i.e., the elderly)[181], may have introduced non-response bias and attenuation of the risk estimates towards the null.[180] In contrast, the age-specific categories of CRF used in Paper III are likely to prevent against such bias, and may partly explain the stronger associations observed for this exposure in relation to VTE risk. Moreover, we appreciate that the incidence rate in the Tromsø Study is comparable to akin populations.[9,11,158]

Traditionally, strong emphasis has been put on the representativeness of the study population in epidemiological research. However, Rothman argues that this is a concern mainly in descriptive and less so etiological research.[176] In the latter, a highly representative sample may pose a threat to the internal validity due to higher risk of confounding and difficulty to obtain uniform precision of measurements. The Physicians' Health Study and the Nurses' Health Study are examples of non-representative study populations from which findings have

been generalized to other settings and populations. Importantly, such generalization is only valid under the assumption that the non-representativeness is independent of the association under study, and knowledge of the underlying pathophysiology is mandatory.[176] Hence, with high internal validity and proper knowledge of the biological mechanisms, generalization despite a non-representative study sample may be acceptable.

In Paper III, we observed that individuals who were excluded from the study were older and had a less favourable cardiovascular risk profile, compared with those included. Previous studies have reported that CRF is favourably associated with other health outcomes in these subgroups[182-184], and in Paper II we reported that the association between physical activity and VTE risk was stronger among the elderly. Thus, we believe that the observed association in Paper III is likely to carry over to these less well represented subgroups.

5.1.3 Information bias and misclassification

Errors in epidemiological research may be classified as either random or systematic, and are distinguished by that the former decreases with increasing sample size whereas the latter is unaffected by the size of the study.[185] Bias refers to the tendency of the observed results in a study to differ from the truth, and may arise from systematic error introduced during the planning or recruitment phase (selection bias), the data collection or analysis phase (information bias), or in the publication process (publication bias).[173] Selection bias is a major concern in case-control studies due to challenges in recruiting cases and controls from the same population. However, as briefly discussed in the former section (5.1.2 External validity), it also demands attention in cohort studies when the selection or participation is somehow related to the association under study.

Information bias occurs when erroneous information, either on exposure or outcome variables, is obtained about study participants. The subsequent misclassification is termed differential or non-differential, depending on whether or not it depends on other study variables.[185] As the exposure information in the Tromsø Study is collected prior to the occurrence of disease, potential misclassification in the present thesis is likely to be unrelated of the outcome (i.e., non-differential). Such misclassification most often leads to an underestimation of the association.[173]

Potential sources of information bias in the present thesis include the use of self-administered questionnaires, measurements obtained by study personnel or machines, and incomplete medical records. Information on the main exposure variable, physical activity, was

obtained through self-administered questionnaires. This method has several strengths such as cost-effectiveness and feasibility, but also important weaknesses such as the susceptibility to error due to lack of memory or social desirability and generally have a lower accuracy compared with objective methods.[105] As described in section 3.2.1, the validity and reliability of the physical activity questionnaires used in the Tromsø Study was addressed in a subsample of participants in the HUNT study.[164,165] For the questionnaires in Tromsø 4 and 5, the validity of the hard physical activity question was acceptable, whereas that on light physical activity was less well correlated with the comparison measures.[164] The questionnaire used in Tromsø 6 was reported to correlate well with the comparison methods.[165] Likewise, the algorithm used in Paper III, has been reported to be a valid tool for estimation of CRF.[166]

Importantly, the evaluation of validity and reliability of the questionnaires used in Tromsø 5 and 6 was conducted among men aged 20 to 39, and a pertinent question is whether these findings apply to a general population.[164,165] In particular, elderly may have challenges with cognition or disability, and questionnaires developed and validated in a young population may not be appropriate to use in an older population.[186] As discussed and demonstrated in Paper I, a method for indirect validation of an exposure variable is to test its association with another outcome with a well-established association with the exposure variable. The physical activity variable used in Papers II and IV was associated with the risk of MI in an expected manner, which supports the validity of the variable. Likewise, the categories based on physical activity and CRF were related to cardiovascular risk factors in a meaningful way in Papers II and III. Therefore, we assume that the main exposure variables in the present thesis are not prone to information bias to a significant extent, and, if present, the non-differential nature of misclassification would lead to an underestimation of the reported associations. Notably, there may also be misclassification of confounders used in the present thesis (e.g., BMI, education, smoking, disease history), which potentially could lead to incomplete adjustment and residual confounding.[173] As BMI was measured in a standardized way by trained personnel in the Tromsø Study, we expect misclassification to be a minor concern for this variable.

Information bias is also relevant for the outcome variable. The VTE cases in the present thesis were recorded retrospectively through searching the hospital discharge registry, the autopsy registry and the radiology procedure registry at UNN. This hospital is the only provider of hospital care in the study region (>200 km radius), which facilitates for the development of comprehensive registries of conditions managed in hospitals. Further, the strict criteria for adjudication of cases reduce the possibility of false positive cases. Nevertheless, despite efforts

to ensure a complete register, there is a chance that cases may have been missed. Due to low autopsy rates in Norway, some PEs presenting as sudden death may not be registerered.[187] Further, VTEs occurring during travel may have been missed initially, but were most likely recorded during follow-up visits in the outpatient clinic. We believe that the extent of this problem is minimal. In addition, it is unlikely that cases that were missed differ substantially from those that were recorded in terms of baseline characteristics, and potential bias would be non-differential.

5.1.4 Modifiable risk factors and regression-dilution bias

In prospective studies on modifiable risk factors, the exposure status of study participants may change during follow-up. If not accounted for, this may introduce regression dilution bias with underestimation of the true association and potentially type-II errors.[188] It is well established that physical activity and CRF decrease with age [189], and studies with a long follow-up based on baseline data are highly susceptible to misclassification of study participants on these variables. A Danish study investigated the association between physical activity and the risk of premature mortality, and reported that the association was markedly stronger (24-59%) when changes in behavior during follow-up were accounted for.[190]

In Paper I, we discussed this challenge in the context of physical activity and VTE risk. A striking observation in the literature was that studies reporting null findings tended to have longer follow-up compared with those that reported an association. Additionally, a previous report from the Tromsø Study using the traditional time-fixed approach did not observe any association between physical activity and VTE risk during 12.5 years of follow-up.[153] Therefore, we designed Paper II with the aim to address this issue by the use of repeated measurements and time-varying analyses. Here, participants who attended multiple surveys had their exposure and confounder data updated at each time point, and contributed with observation periods corresponding to the number of partaken surveys (Figure 5). This yielded a median duration of the observation periods of approximately 7 years, which is relatively short in the context of cohort studies. By the use of this approach, we found that regular physical activity was associated with a 23% lower risk of incident VTE. Thus, there is chance that previous studies on physical activity and VTE risk using a time-fixed approach may have underestimated or even missed an association between physical activity and VTE risk.

In Paper III, the mean duration of follow-up was relatively short (8.5 years), which lowers the extent of potential regression dilution bias and time-varying analyses were not applied. In Paper IV, we used the activity level from the survey before the incident VTE event

to investigate the association with major complications after VTE. The median duration between data collection and incident VTE was 5.5 years, and an additional 3 to 4 years of follow-up between incident VTE and potential recurrence or mortality. The potential for changes in physical activity during follow-up relate to both age or time, and the experience of an acute VTE event. In a subgroup of participants, we investigated whether physical activity before the incident VTE event were representative for the level of activity after the event. We found that 75% remained at the same level, whereas 18% decreased and 7% increased their level of physical activity. We acknowledge that the presence of non-differential misclassification is likely, and the reported risk estimates may be underestimated.

5.1.5 Confounding and mediation

Confounding refers to a situation where a non-causal association between an exposure and an outcome is observed, but can be attributed to the influence of a third variable (i.e., the confounder).[173] A confounder is causally associated with the outcome and non-casually associated with the exposure, and is not an intermediate in the causal pathway.[173] The presence of confounding may strengthen, weaken or reverse the association under study.[173] The phenomenon is a major concern in observational studies where the non-random allocation to exposure groups may lead to unbalanced distribution of confounding variables between groups. Although confounded associations are not regarded as biased, proper identification and handling of confounders are important to avoid implementing spurious associations in a causal context.[173] The most common strategies to deal with confounding in cohort studies are multivariable regression analysis and stratification. The selection of potential confounders is based on a priori knowledge, and the presence of confounding is evaluated and verified by the data. In the present thesis, we used both multivariable regression and stratification to control for confounding.

Age, sex, body weight, socioeconomic status, cancer and CVD are potential confounders of the association between physical activity and VTE as well as CRF and VTE. In Paper II, we evaluated the association between physical activity and VTE risk by multivariable regression in three different models; the minimally adjusted model included age (as timescale) and sex, thereafter BMI and history of CVD and cancer were successively added to the model. This approach yields risk estimates that are adjusted for all covariates in the model, and a main advantage is that data from all participants is used thereby maintaining statistical power.[191] Age was used as timescale in the regression model, with the age at inclusion defined as entry time and the age at VTE or censoring defined as exit time. Alternatively, time on study may be used

as timescale, and age can be included as a covariate in the regression model. We regard that VTE risk is more strongly associated with age than with time on study, and thereby using age as timescale ensures a more effective control of its effect.[192,193] We found that adjustment for BMI attenuated the risk estimates by 7 to 12%, whereas additional adjustment for comorbidities did not alter the risk estimates. Although residual confounding by unknown or unmeasured confounder cannot be eliminated, our results are suggestive that the association is independent of cancer and CVD.[173] In contrast, in the main analysis, the association between physical activity and VTE was not significant after adjustment for BMI. However, as BMI may be an intermediate in the causal pathway, it may not be appropriate to adjust for this variable. The role of BMI as a mediator in this context will be revisited shortly.

In Paper III, we adjusted the analyses of the association between fraction of age-predicted CRF and VTE, as well as METs and VTE, for age (as timescale) and sex. However, as the third exposure variable, age- and sex-specific categories, by definition ensured that the distribution of age and sex is equal between the groups, we did not additionally adjust this regression model for sex. In a second model, we additionally adjusted for smoking, education, CVD and cancer. The risk estimates remained essentially unchanged, suggesting that these variables were not confounders or mediators of the association. Further, we evaluated the impact of body weight status on the association between fraction of age-predicted CRF and VTE by stratification, while simultaneously adjusting the regression model for age (as timescale) and sex. In this approach, the study population is divided into subgroups based on the potential confounder (body weight status), and the association was assessed within each group. Although the strategy reduces potential confounding through more similar comparison groups, it comes at the cost of statistical power.[191] We found that the association between CRF and VTE was independent of weight status. Again, due to the observational design, the chance of residual confounding remains. As CRF has a considerable genetic component, we proposed the use of Mendelian Randomization studies to explore a potential causal relationship.[194,195]

In Paper IV, we addressed the association between physical activity and the risk of recurrence and all-cause mortality in VTE patients. The former association was evaluated in two regression models; the minimally adjusted included age, and the multivariable model included BMI, history of CVD and cancer-related VTE. There was no association between physical activity and the risk of recurrence, and the risk estimates were essentially similar in both models. In the context of physical activity and the risk of mortality after VTE, we included smoking and education as additional potential confounders.[196] We found that physical activity

was associated with a lower risk of mortality after VTE, and that the association was independent of BMI, smoking and education, but partly explained by history of cardiovascular disease and cancer-related VTE. In this paper, time on study was used as time scale in the recurrence analyses, and age in the mortality analyses. The rationale was based on the strength of the association between timescale and the outcome (e.g., the risk of recurrent VTE was regarded to be more strongly dependent on time on study than on age, and opposite for mortality).[193]

In Paper I and II, we addressed the potential mediating role of BMI in the context of physical activity and VTE (Figure 6). Traditionally, BMI has been regarded as a confounder of the association between physical activity and VTE.[8,144,147] However, as physical activity is important in weight management[197,198], we argue that BMI (and presumably other weight measures) may be in the causal pathway, and should rather be treated as mediators of the association. A mediator is defined very similar to a confounder, with the exception that the mediator is a presumed causal consequence of the exposure.[199] Adjusting in the causal pathway leads to underestimation of the true association, and is inappropriate unless the aim to explore alternative mechanism for an association.[173,199]

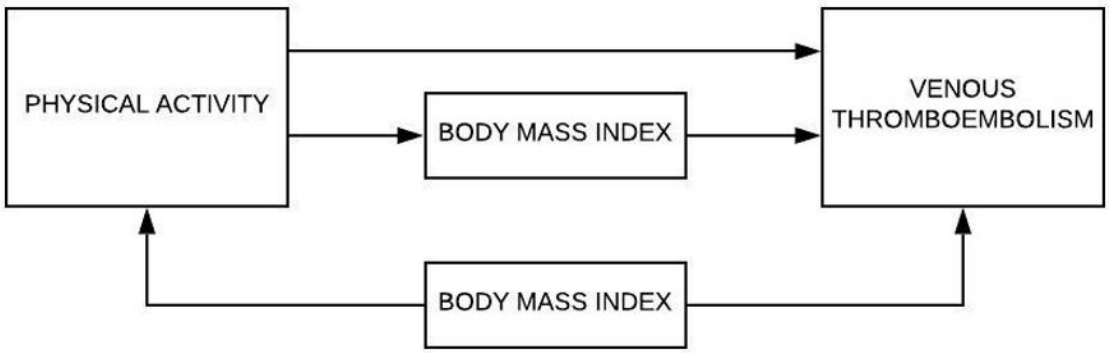

Figure 6 Plausible pathways for the association between physical activity and VTE, and the role of BMI as an intermediate (middle) or a confounder (bottom)

Mediation analyses can be used to evaluate how an intermediate variable relates to the association between an exposure and an outcome. This includes either comparing regression models with and without the mediator, or by use of the counterfactual framework. The latter approach allows for partitioning the total effect into a direct and indirect component.[200] In Paper II, we aimed to quantify to what extent the association between physical activity and VTE risk was mediated by BMI (indirect effect). We used the counterfactual approach based on Aalen's

additive hazard model developed by Lange & Hansen[201], and found that 14 to 36% of the association was mediated by BMI. On this basis, we may conclude that the data are consistent with a mediating role of BMI in this context, although the association between physical activity and VTE risk may primarily be ascribed to other mechanisms. The absence of unmeasured confounders is an important assumption in the interpretation of mediation analyses, and careful planning of the statistical model is vital.[201] Although the analysis in Paper II was adjusted for two important confounder; age and sex, we acknowledge that residual confounding can never be eliminated in observational research. It is also important to note that our mediation analysis was based on cross-sectional data, and assumed that BMI was determined by physical activity. However, we cannot rule out that physical activity levels were influenced by BMI, and our findings need to be confirmed in studies with a clear temporal sequence between these variables.[199] Limitations of our analysis were emphasized in the discussion section of Paper II.

5.1.6 Interaction

Statistical interaction describes a situation where two or more risk factors modify the effect of each other with regard to the occurrence of an outcome, and is also referred to as effect modification.[173] The presence of interaction leads to variation in the risk estimates across strata, and failure to address interaction may lead to the reporting of risk estimates that are not applicable to all strata.[173] In the present thesis, we tested for interaction by including cross-product terms between the exposure variables and sex, BMI and age (only in regression models with time on study as time scale) in the regression models, and no interactions were found. However, in Paper II, we stratified the analyses by the age of the participants (<65 and ≥65 years) in the absence of formal interactions, because previous studies suggested that age might be an effect modifier of the association between physical activity and VTE risk. Further, in Paper IV, we stratified the analyses on sex, because of the difference in the baseline risk of recurrence between men and women, even though no formal interaction was present. Although the confidence intervals overlapped, the point estimates suggested that the relative risks were different in men (HR 1.48; 95% CI 0.83-2.65) and women (HR 0.95; 95% CI 0.52-1.74).

5.1.7 Missing data

Missing observations are common in both epidemiological and clinical research, and may occur due to technical failures, errors in the handling or loss of laboratory samples, inadequate response to questionnaires or failure to adhere to the study procedures.[202] Although, a few missing observations are unlikely to pose a threat to the integrity of a study, there is no consensus on the upper limit of “acceptable” missingness. Further, it has been suggested that

the pattern of missing data is more important than the extent.[203] However, the reasons for missingness are often beyond the control of the researcher and may be difficult to identify. As none of the strategies to deal with missing data are completely satisfactory, it is important to maximize a comprehensive data collection. If the extent of missing is large, omitting the variable is the best option. However, if the extent of missing is trivial, study participants with missing values may be omitted, either partly (available case analysis) or completely (complete case analysis). Finally, the missing value of a variable may be estimated (imputed) from the available data.[202] The main concern with missing data is whether the available data are biased, but also loss of precision and power.[202] If study participants with missing data differ significantly from those with data, deletion may yield biased results. In contrast, if the missingness is unrelated to the value itself and the available data (i.e., missing completely at random), valid results can be anticipated.[202] Imputation requires the assumption that the missingness is at random (i.e., unrelated to the value itself, but related to other variables in the dataset) or missing completely at random. Importantly, it is not given that imputation yields the correct value of the missing variable.[203]

In Paper II-IV, those with missing data on the exposure variable were excluded, whereas those with missing data on confounders were omitted from these analyses only. In Paper II, the extent of missing data on the main exposure variable was regarded as minor (1%) and deletion was not expected to compromise statistical power or introduce selection bias. As the extent of missingness was larger in Paper III (18%), we compared the included and the excluded participants, and found that those excluded were older and had a less favorable cardiovascular risk profile. However, as discussed in chapter 5.1.2, we do not believe that selection bias has been introduced due to deletion of participants with incomplete data. In Paper IV, the extent of missingness on the exposure variable was intermediate (8%). Although, we did not perform a comparison between included and excluded VTE patients in the paper, a post-hoc comparison with all VTE patients in the Tromsø Study revealed that our study sample was comparable on key variables (i.e., age, sex, clinical presentation, provoking factors).[158] Overall, missing data on confounders were of a small extent (<2.5%) throughout Papers II-IV, and omitting participants in multivariable analyses is not expected to introduce bias or compromise study power.

5.2 Discussion of main results

5.2.1 Physical activity and incident venous thromboembolism

Prior to the present thesis, the literature on the association between physical activity and risk of incident VTE was conflicting. Whereas a beneficial association was observed in some studies[8,144,146], others reported an adverse association[2,152] or no association.[153,154] In Paper I, we reviewed the literature and suggested potential explanations for the observed inconsistency, and these were related to assessment strategy, study design and data handling. First, a striking observation was that all studies with retrospective assessment of physical activity reported an inverse association between physical activity and VTE risk.[149-151] Such studies are prone to recall bias and may overestimate the true association.[172] We further noted a trend among the prospective studies that those reporting an association between physical activity and VTE risk had shorter duration of follow-up compared with studies that reported null findings. This led to a discussion on a prime concern in prospective studies; underestimation of associations due to regression dilution bias.[188] Finally, although the majority of previous studies regarded BMI as a confounder of the associaiton[8,144], we argued that BMI may be considered as a mediator in this context.

In Paper II, we addressed these issues through appropriate study design and data analysis. Regression dilation bias was minimized by updating the data on participants who took part in several surveys, and the duration of the observation periods was kept relatively short. We also quantified the mediating role of BMI using the Aalen's additive hazard model. We found that regular physical activity (≥1h per week) was associated with a significant 23% lower risk of incident VTE, which was strongest in the elderly (30% lower risk) and in relation to provoked events (34% lower risk). The largest benefit occurred at a low amount of weekly physical activity. The risk estimates were expectedly attenuated (by 7-12%) after adjustment for BMI, whereas further adjustment for CVD and cancer did not influence the risk estimates. Only a moderate proportion of the association was mediated via BMI. The study not only provided fresh data to the debate on whether regular physical activity may protect against incident VTE, but also information to what extent the association was mediated by body weight status.

Although a comparison of risk estimates with other studies is challenging due to different methodology, our results are in line with those previously reported from several cohorts, including the ARIC study[144], the REGARDS study[146], the Million Women study[8], the

MESA study[145] and the IWHS.[147] In these reports, physical activity was associated with 16-41% lower VTE risk prior to BMI-adjustment. Succeeding our study, one report from the Swedish Venous thromboEmbolism In Northern Sweden (VEINS) cohort has been published.[204] Johansson and colleagues[204] found that both leisure time and occupational physical activity was associated with lower risk of incident VTE in women, whereas no association was observed in men. Women who performed leisure time physical activity once or more per week had 21% lower risk in the age-adjusted model. After additional adjustment for BMI, hypertension, smoking education and cancer, the risk reduction was 17%. In the overall cohort, leisure time physical activity was associated with 10 to 19% lower risk in the basic model and 7 to 13% lower risk in the fully adjusted model. Previous population-based cohorts reporting sex-specific data have not found notable differences between men and women[153,154], and sex was not identified as an effect-modifier in Paper II. Nevertheless, future studies may follow this lead and evaluate potential sex-differences in the association between physical activity and VTE.

A focus in Paper II was to explore the role of BMI as a mediator of the association between physical activity and VTE risk. The most common approach in the previous literature was to include BMI as a confounder, and to conclude on basis of BMI-adjusted risk estimates.[8,144,147,204] A confounder is defined as a variable that is non-casually associated with the exposure, causally associated with the outcome, and not an intermediate in the causal pathway.[173] The difference between a confounder and a mediator is that a mediator is presumed to be a causal consequence of the exposure *and* causally associated with the outcome (i.e., in the causal pathway).[199] In Paper I and II we argue that BMI meets the definition of a mediator in this context, and in Paper II we reported that 14-36% of the association between physical activity and VTE was mediated via BMI. Thus, adjusting for BMI would underestimate the true association. Adjusting in the casual pathway is regarded as inappropriate unless the aim is to evaluate alternative mechanisms.[173,199] The risk estimates for the association between physical activity and VTE are typically attenuated by 3-24% after adjustment for BMI.[8,144,147] Although the data in Paper II are consistent with a mediating role of BMI, distinguishing between a mediator and a confounder cannot be done statistically, but relies on conceptual consideration.[199] This is a complex matter, and as the association between physical activity and BMI may be bidirectional, one may argue that BMI also qualifies as a confounder.[205]

Up to now, the principal focus has been to establish whether there is an association between physical activity and the risk of incident VTE, and a next step would be to characterize

the shape of the association. Apart from the REGARDS study, the current literature suggest that the largest benefit occur at a relatively low amount of physical activity, and that the additional yield with higher amounts of activity is modest.[8,144,146,204] Moreover, data from the CHS[152] and the Million Women study[8] suggested that a high amount of strenuous physical activity may be associated with an increased risk of VTE. In the CHS, a cohort of elderly (≥ 65 years), participation in strenuous physical activity was associated with 75% higher risk of incident VTE compared with no exercise.[152] This apparently contrasts the findings in Paper II where the beneficial association was strongest among the elderly participants. We speculate that the discrepancy may be explained by different methodology between the studies. Importantly, as information on physical activity primarily is collected as categorical data, the precision is limited, and may mask variation within categories.[206]

On basis of the available data, we may conclude that regular physical activity is associated with a moderately lower risk of incident VTE. The benefit occurs at a relatively low amount of activity and is not dose-dependent. Pathways related to BMI seem to explain only a moderate proportion of the association. Due to the high prevalence of inadequate physical activity in the population, it is likely that a successful population strategy to increase physical activity levels would reduce VTE incidence.[181]

5.2.2 Cardiorespiratory fitness and incident venous thromboembolism

Prior to the present thesis, the association between CRF and the risk of incident VTE had been addressed in two studies restricted to men, of which one reported a significant inverse association between CRF and VTE risk[156] and one were suggestive of an inverse association.[157] In Paper III, we found that individuals with eCRF ≥85% of age-predicted had 46% lower risk and those with eCRF >100% of age-predicted had 67% lower risk, compared with those with <85% of age-predicted eCRF. The association was independent of sex, age, smoking, education, CVD and cancer, and remained when eCRF was expressed as an absolute value (METs) and in age- and sex-specific categories.

As for the reports on physical activity and VTE risk, a direct comparison with previous publications is challenging due to different methodology. However, our findings are in accordance with a Swedish registry-based study of male conscripts (18 to 20 years). Zöller and colleagues[156] found that each one SD increase in CRF, assessed as maximal workload on a cycle ergonometric test ($Watt_{max}$/kg), was associated with 24% lower risk of unprovoked incident VTE in the univariate model and 19% lower risk after adjustment for BMI.[156] An important limitation of the study was that the low mean age at incident VTE (42 years), which may hamper

the generalizability. In the Finnish Study (KIHD) Kunutsor and colleagues[157] found that men in the highest tertile of CRF, assessed directly as maximal oxygen uptake (ml/kg/min) on a cycle ergonometric test, had a non-significant 20% lower risk of incident VTE compared with those in the lowest tertile. The risk estimate was essentially similar (18% lower risk) after adjustment for several established cardiovascular risk factors (not BMI) and other comorbidities. The risk in the middle tertile was essentially similar as the reference group. For the highest tertile, the association was stronger (28% lower risk in the fully adjusted model), but non-significant after correcting for within-person variability using a regression-dilution ratio.[157] The authors speculated that an association still may have been camouflaged due to a long follow-up (25.5 years), limited statistical power and study population characteristics.[157] In extension of these two publications, Paper III makes an important contribution to the field of lifestyle factors and VTE risk by showing an inverse association between eCRF and incident VTE in a population-based cohort with a wide age-range, across VTE subtypes and body weight categories.

In stratified analyses, we found that the risk of VTE was comparable in normal weight and overweight/obese individuals with eCRF <85% of age-predicted, and having an eCRF ≥85% of age-predicted was associated with similar risk reductions in normal weight (55% lower risk) and in overweight/obese (50% lower risk) individuals. This suggests that the association between eCRF and VTE risk is independent of weight status, and, interestingly, that eCRF appears to mitigate the elevated risk associated with overweight/obesity. This is in line with the findings in the Swedish study where the risk estimates were only marginally attenuated after adjustment for BMI[156], and goes along with our findings in Paper II. Overweight and obesity are well-established risk factors of VTE, and the risk increases in a dose-dependent manner across the BMI-spectrum.[75] It is also an impactful risk factor due to a high prevalence, and it is estimated that almost one third of unprovoked VTEs can be attributed to a high BMI.[72] As CRF and body weight are modifiable through physical activity, exercise interventions may represent an important measure to lower the burden of VTE in this high-risk group.[198]

The available literature suggest that CRF may be more strongly associated with VTE than physical activity. As the two exposures are related, it is challenging to disentangle their effects and conclude on which is more important.[207] In the context of arterial CVD and mortality, Blair and colleagues[207] suggested that the most likely explanation was different methodology as CRF is measured with a higher level of precision and is less prone to misclassification than physical activity. This explanation is equally credible in relation to VTE.

They also noted that, in a public health perspective, it is irrelevant to determine whether physical activity or CRF is more important as recommendations anyway will be aimed at behavior (i.e., physical activity).[207] Importantly, CRF is not only determined by activity levels, but also age, sex, body size and composition, comorbidity and genetic architecture, and it provides valuable information of cardiovascular health and whole-body functional capacity beyond that of physical activity.[114,118] Notably, CRF has been shown to predict post-surgical complications, and, in relation to CVD morbidity and mortality, adding CRF to traditional risk factors improves risk prediction and model performance.[117,208] Hence, CRF has been proposed as a more useful clinical marker than physical activity.[128] Whether CRF may serve as a predictor of VTE in high-risk populations, such as patients with cancer or ischemic stroke, is an intriguing question.[80,209]

5.2.3 Physical activity and major complications after venous thromboembolism

Despite efforts to investigate the association between physical activity and the risk of incident VTE, there was limited data on physical activity in relation to the risk of recurrence and mortality after VTE prior to the present thesis. In Paper IV, we found that regular physical activity (≥1h per week) was associated with 19%, 25% and 28% lower risk of mortality during 1, 5 and 10 years of follow-up, respectively. The association was independent of age, sex, smoking, education, history of CVD and cancer. These findings are in line with those reported from the SWITCO65+-study, which found that patients who reported a low level of physical activity had a nearly two-fold higher risk of mortality during three years of follow-up.[160] Paper IV makes an important extension to this study by demonstrating that physical activity is associated with a lower mortality risk across ten years of follow-up in VTE patients of a wide age-range recruited from a general population.

A large body of evidence support an inverse association between physical activity and the risk of premature mortality.[4,210,211] This is established in general populations, across age, sex, race, weight status, and extends to patients groups such as those with arterial CVD and some cancers.[4,210,211] A comprehensive report from the 2018 Physical Activity Guidelines Advisory Committee concluded that any amount of physical activity is better than none, that the majority of benefit occur at the low end of the activity spectrum, and that there is no evidence of increased risk associated with high amounts of physical activity (up to 3 to 4 times of the current guidelines).[4] The maximum risk reduction is typically reported to be 40% in studies based on self-reported physical activity.[4,210,211] This is in line with the findings in Paper IV, where the largest risk reduction occurred between the reference group and those reporting physical activity at least one hour per week, and with limited benefit with higher amounts of

physical activity. Interestingly, Ekelund and colleagues[112] recently published a meta-analysis of studies using accelerometer assessed physical activity and all-cause mortality. They reported effect sizes up to 70%, and suggested that previous studies using self-report data were prone to misclassification and underestimation of the association.[112] This implies that, the association between physical activity and mortality in VTE patients may be even stronger than reported in Paper IV.

Although accumulating data indicate that physical activity is associated with a lower risk of incident VTE, the findings in Paper IV suggest that there is no association between physical activity and the risk of recurrent events. However, in sex-stratified analyses, a non-significantly higher recurrence risk was observed in physically active men. Due to the difference in mortality risk between active and inactive individuals, we also performed competing risk by death-analyses, and reached the same conclusion. Paper IV was the first, and to date the only, study to investigate the association between physical activity and the risk of recurrence. However, a previous reported based on the MEGA study investigated the association between a sedentary lifestyle (prolonged sitting) and recurrence risk. During a mean follow-up of five years, a sedentary lifestyle was associated with 1.5-fold increased risk in women, whereas no association was observed in men. As physical activity and sedentary behavior are distinct in terms of physiological adaptations and should be regarded as separate risk factors[130,212], the findings from the MEGA study are not directly comparable to those in Paper IV. It is not unusual that a risk factor apparently is differently related to first and recurrent events, and this phenomenon is termed the "recurrence paradox".[213,214] An important realization is that the risk of incident and recurrent events are compared on different scales.[213] Thus, the association between a risk factor and the outcome may appear differently, although the absolute impact may be similar.[213] The recurrence paradox may occur because the participants are selected on basis of the outcome, which introduces dependence between risk factors in the selected sample (that is not observed in the general population). This is called index event bias (also known as collider bias), and may introduce underestimated or reversed associations.[214]

In Paper IV, we investigated the association between physical activity *prior* to incident VTE and the risk of recurrence and mortality. Although we were able to demonstrate an association with mortality risk, a relevant question is whether and how physical activity habits change after VTE. Current evidence support early mobilization after acute VTE, as it may lower the risk of PTS, minimize physical deconditioning and improve quality of life.[215-217] However, there is limited long-term data on changes in physical function and physical activity habits. In

Paper IV, we observed that, in selected patients who returned to a survey after the incident event, 75% remained in the same activity category, whereas 18% decreased and 7% increased their physical activity. In a Canadian study of 100 patients with incident PE, Kahn and colleagues[218] investigated the course of functional and exercise-related variables. CRF was assessed at 1-month and 12-months after PE. Although the majority improved their CRF during follow-up, almost half of the patients still had CRF less than 80% of predicted one year after the PE. Unfortunately, there was no control group and it is not known to what extent the CRF changed during in the first month after the PE event.[219] In the NHS, physical function was compared in women with and without VTE, and it was reported that a VTE event was associated with a significant decline in physical function equivalent to more than five years of aging.[220] A small qualitative study in patients with acute PE reported that fear of complications during exercise was a barrier, particularly among those with limited previous experience with physical activity.[221] In summary, these data suggest that there may be a need for structured rehabilitation in patients with VTE. Interestingly, a recent publication proposed a framework for the development and implementation of a tool for assessing functional outcomes in patients with VTE.[222] Although the current data are limited, exercise interventions are reported to be safe and feasible in selected patients with VTE.[223,224] While this may not influence the recurrence risk, the benefits of an active lifestyle are extensive.[4]

6 Conclusions

- In the literature review, we concluded that available evidence indicated that regular physical activity was associated with lower risk of incident VTE, but not in a dose-dependent manner. However, the large variation in assessment methods challenged the comparison between studies. We suggested that future studies should use objective assessment strategies and account for fluctuations in physical activity during follow-up. We proposed several biological mechanisms that may explain an association between physical activity and VTE, and these related to all aspects of Virchow's triad. Data on the role of physical activity in relation to recurrence and VTE related complications were scarce, and we concluded that there was a need to explore the necessity and potential benefits of structured rehabilitation in the VTE setting.

- We found that regular physical activity was associated with a lower risk of incident VTE, particularly in the older participants (≥65 years) and in relation to provoked events. The association was independent of age, sex, CVD and cancer. The benefit occurred with a low amount of weekly physical activity (≥1 hour), with little evidence of added benefits with increasing amounts of activity. Weight status (BMI) mediated a moderate proportion of the association, but the majority of the effect is likely explained by other mechanisms.

- Higher eCRF (≥85% of age-predicted) was associated with a lower risk of incident VTE, and this association was stronger and more consistent compared with physical activity. The association was independent of age, sex, smoking, education, CVD, cancer and BMI, and our findings suggested that eCRF may mitigate the elevated VTE risk associated with a high body weight.

- Regular physical activity (≥1 hour per week) was associated with a lower risk of mortality after incident VTE, particularly in those with DVT. The association remained for at least ten years after the incident event and was independent of age, sex, BMI, smoking, education, cancer and CVD. In contrast, physical activity was not associated with the risk of recurrent VTE, either in traditional Cox regression models or in competing risk by death-analyses.

7 Final remarks and future perspectives

Emerging data, including the present thesis, support that a lower risk of incident VTE is among the numerous benefits of regular physical activity and maintaining an adequate level of CRF. The Norwegian Directorate of Health recommends that adults and elderly perform at least 150 minutes of moderate intensity or 75 minutes of high intensity physical activity per week, or a combination of this. However, only one third of adults in Norway and worldwide achieve the recommended amount, and physical inactivity is now a global pandemic.[181,225] Due to the high prevalence of inadequate physical activity, the absolute impact and preventive potential is enormous.[226] Nevertheless, an important message in the context of VTE and other health outcomes is that large benefits can be harvested with relatively little efforts, probably also below today's recommended amount.[4,107,112]

The findings in the present thesis challenge the common perception that the effect of physical activity is largely explained by body weight. We also show that CRF may counterbalance the elevated VTE risk that accompanies a high body weight. VTE is a multicausal disease with numerous interacting factors, which implies several potential target points for prevention. As both body weight and CRF can be modified by physical activity[198], it is plausible that strategies to promote physical activity may have added benefit on the burden of VTE among overweight and obese individuals.

Although self-administered questionnaires are regarded adequate methods for assessment of physical activity, several novel approaches have been developed. Both accelerometer-based assessment of physical activity and objective measures of physical capacity are reported be superior health predictors compared with self-reported physical activity.[112,128] We hope that the associations between physical activity, CRF and VTE will receive attention in future studies applying such methods, as this may contribute to an increased and more nuanced understanding.

The role of physical activity in relation to major complications after VTE is largely unexplored. However, the available literature suggests that patients with VTE may benefit from such interventions. Physical activity is now implemented as an important component in the treatment and rehabilitation phase of arterial CVD and some cancers, and we welcome studies exploring the need and effect of such interventions in the VTE setting.

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PAPER I

Regular Physical Activity and Risk of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) is a complex multifactorial disease that represents a growing public health concern. Identification of modifiable risk factors at the population level may provide a measure to reduce the burden of VTE. In this review, we summarize current knowledge of the role of physical activity on the risk of VTE and VTE-related complications. We also discuss methodological challenges related to research on physical activity, and put forward plausible mechanisms for an association between physical activity and VTE. Up to now, published studies have reported diverging results on the relationship between physical activity and VTE, and a complex picture has emerged. However, the available evidence appears to be balanced toward a small beneficial effect of physical activity on the risk of incident VTE, but not in a dose-dependent manner. Still, the lack of an operational definition and standardized assessment method for physical activity, as well as several sources of bias, impairs the interpretation of the available literature. Additional work is necessary to understand the role and how to apply physical activity in the VTE setting. Future research should utilize objective assessment strategies of physical activity and physical fitness, account for the fluctuating nature in habitual activity levels, and explore the role of physical activity in the areas of secondary prevention and VTE-related complications.

Keywords
- physical activity
- risk factor
- venous thromboembolism
- review

Despite improved knowledge of risk factors and preventive strategies, recent findings imply that the incidence of venous thromboembolism (VTE) has remained steady or slightly increased over the past decades.[1,2] Moreover, with increasing prevalence of important risk factors, such as cancer, obesity, and an aging population, we may anticipate a further rise in the incidence of VTE in the years to come.[3–6] Hence, there is a great need to identify and take action on modifiable risk factors to combat the growing burden of VTE.

Initiated by the seminal study in 1953 by Morris et al[7] on the association between occupational physical activity and coronary heart disease, researchers in the field of physical activity epidemiology have established a firm dose-dependent inverse association between physical activity and risk of arterial thrombotic disease.[8,9] There is also overwhelming evidence that regular physical activity is associated with a reduced risk of premature all-cause mortality, type-2 diabetes, and some types of cancer.[8,10,11] Nevertheless, a significant amount of the population worldwide fails to meet the minimum recommendations for physical activity, and physical *in*activity is now referred to as a global pandemic.[12,13]

Whether physical activity influences the risk of incident VTE is debated, and limited data exist on the role of physical activity in the prevention and treatment of VTE-related complications, such as recurrence, postthrombotic syndrome (PTS), and chronic thromboembolic pulmonary hypertension (CTEPH). The focus of this review is to summarize the existing epidemiological evidence on the association between physical

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activity and risk of VTE. We will also discuss methodological challenges related to research on physical activity, and put forward plausible mechanisms for an association between physical activity and VTE. The potential role of physical activity in the prevention of recurrent disease, PTS, and CTEPH will also be addressed. In addition to an analytical review of the existing literature, we will substantiate the discussion with results from a large Norwegian prospective cohort, the Tromsø study.

The PubMed database was searched for articles on regular physical activity and VTE risk by using combinations of the terms "physical activity," "physical inactivity," "venous thromboembolism," "deep vein thrombosis," and "pulmonary embolism." Relevant publications were also identified through PubMed links and by cross-referencing from the reference lists of the retrieved papers.

Epidemiological Evidence: Physical Activity, Sedentary Behavior, and Risk of Incident VTE

Immobilization is a well-recognized risk factor for VTE, and logically, several researchers have hypothesized that a sedentary lifestyle or lack of regular physical activity could be associated with an increased risk of VTE. However, the reported results so far have shown an inconsistent pattern (►**Table 1**).

In a large prospective cohort, the Atherosclerosis Risk in Communities (ARIC) study,[14] middle-aged men and women participating in moderate or high amounts of physical activity had 19 to 31% lower risk of VTE compared with those with a low amount of physical activity. Similarly, in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study,[15] participation in physical activity one to three times and more than three times per week was associated with 30 and 41% lower risk of VTE, respectively. In the Million Women study, Armstrong and colleagues[16] found that women who engaged in weekly physical activity had 4 to 34% lower risk of VTE compared with inactive women. However, apart from the REGARDS study[15] where a dose–response relationship was observed, these studies provided limited evidence for a progressive risk reduction with increasing amounts of physical activity.[14–16] On the contrary, in the Million Women study,[16] there was a trend of a small increased risk of VTE in women participating in strenuous physical activity daily, when compared with women who were mostly inactive. Similarly, results from the Cardiovascular Health Study (CHS)[17] showed that weekly participation in strenuous physical activity was associated with a 75% higher risk of VTE compared with inactivity in the elderly, while participating in light-intensity exercise was associated with a nonsignificantly lower risk. Results from the Physicians' Health Study[18] indicated a higher risk of VTE with increasing weekly amount of vigorous physical activity, with a stronger association with provoked than unprovoked events. Thus, in contrast to the potential benefits related to low and moderate amounts of physical activity, excessive or highly intense activity might be associated with an increased risk of VTE.

The results from several other large prospective cohorts have suggested that physical activity has no influence on VTE risk. In the Tromsø study,[19] the weekly amount of moderate and high-intensity physical activity did not modify the risk of VTE in the general population during 12.5 years of follow-up. Likewise, results from the Iowa Women's Health Study[20] showed that physical activity was not associated with VTE risk after adjusting for body mass index (BMI). Moreover, the Longitudinal Investigation of Thromboembolism Etiology (LITE),[21] the Nurses' Health Study,[22] and the Copenhagen City Heart Study[23] all reported no association between physical activity and risk of VTE. These apparently conflicting findings between studies may reflect methodological differences, which is further discussed later.

Sedentary behavior refers to activities that require very low amounts of energy expenditure.[24] Immobilization is an established risk factor for VTE, and essentially all circumstances that are associated with physical restriction, such as bed rest, plaster casts, and paralysis, have been shown to increase the risk of VTE.[25–28] Importantly, highly active individuals may well accumulate large amounts of sedentary time (e.g., sitting time) during a day, and physical activity and sedentary behavior may therefore be regarded as separate risk factors.[24] Using data from the Nurses' Health Study,[22] Kabrhel et al found that women who spent the most time sitting had more than a twofold higher risk of pulmonary embolism (PE). Similarly, in the Multiple Environment and Genetic Assessment (MEGA) study,[29] men and women who were primarily sedentary on a daily basis had 20 and 40% higher risk of VTE, respectively, compared with those who were mostly active. Interestingly, in the Nurses' Health Study,[22] the adverse association with sitting time was most pronounced in women who were also least physically active, suggesting that physical activity to some extent may mitigate the adverse effect of sedentary behavior.

Up to now, the association between objectively assessed physical fitness and risk of VTE has received little attention. However, high maximal aerobic workload (watt) per kilogram body weight on a bicycle test was recently reported to be associated with a lower risk of VTE in men.[30] Moreover, grip strength was reported to be inversely associated with VTE risk in a recently published case–control study of elderly individuals.[31] In summary, the available data are suggestive of a curvilinear relationship between physical activity and risk of incident VTE in which a moderate amount of physical activity may be beneficial, while high amounts of strenuous physical activity may carry no further protection or an increased risk of VTE. Reducing the time spent on sedentary behaviors may also lower the risk of VTE. However, there is considerable heterogeneity between the published studies concerning design, confounding factors, assessment strategies, study populations, and size, which precludes a proper comparison.

Methodological Challenges in Research on Physical Activity and Venous Thromboembolism

There are several aspects to consider related to study design, assessment strategy, and data handling in the conduct and

Table 1 Overview of prospective studies investigating the association between physical activity or sedentary behavior and the risk of incident VTE listed according to main findings

First author (year)	Cohort	Study population	VTE-events	PA assessment[a]	Reassessed PA	Follow-up	Main findings	Confounders	Comments
Beneficial association									
Armstrong (2015)[16]	Million Women Study	Women, 50–64 y	14,550	Five categories of weekly frequency of any and high-intensity PA (sweating/fast heart rate)	No	9 y (first 4 y excluded)	Any PA vs. inactive: 4–18% lower risk Strenuous PA vs. inactive: 8–17% lower risk (**U**-shaped)	BMI (by age), smoking (by age), alcohol (by age), socioeconomic status and region	
Kabrhel (2011)[22]	Nurses' Health Study	Women, 30–55 y	268 (PE only)	Five categories based on weekly METs (calculated from hours/week spent in various activities). Five categories of sitting time based on sitting hours per week	Yes[b]	18 y	HR 2.34 (1.30–4.20) for the highest vs. lowest category of sitting time	[c]	PA above the median partly attenuated the negative effect of sitting time
Olson (2015)[15]	The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study	Men and women, 45 y and older	263	Three categories based on weekly frequency of PA (intensity and duration not provided)	No	5 y	HR for PA 1–3 times/week vs. none: 0.70 (0.53–0.93), HR for PA $\geq$4 times/week vs. none: 0.59 (0.43–0.81)	Age, sex, income, education, race, and region	The highest PA category was associated with 35% lower risk in the BMI-adjusted model
Wattanakit (2012)[14]	The Atherosclerosis Risk in Communities (ARIC) Study	Men and women, 45–64 y	468	Four categories based on the Baecke Sports Questionnaire	Yes	15.5 y	HR PA cat. 2 vs. 1: 0.72 (0.53–0.93), HR PA cat. 3 vs. 1: 0.74 (0.58–0.95). HR PA cat 4 vs. 1: 0.81 (0.62–1.06)	Age, race, ARIC field center, sex, and BMI	All categories were associated with a significantly lower risk of VTE prior to BMI adjustment
Adverse association									
Armstrong (2015)[16]	Million Women Study	Women, 50–64 y	14,550	Five categories of weekly frequency of any and high-	No	9 y	RR for strenuous PA daily vs. none 1.08 (0.99–1.17)	BMI (by age), smoking (by age), alcohol (by age),	

(*Continued*)

Table 1 (*Continued*)

First author (year)	Cohort	Study population	VTE-events	PA assessment[a]	Reassessed PA	Follow-up	Main findings	Confounders	Comments
				intensity PA (sweating/fast heart rate)				socioeconomic status and region	
Glynn (2005)[18]	Physicians' Health Study	Men, 40–84 y	358	Six categories based on weekly frequency of vigorous exercise (sweating)	No	20 y	RR 1.09 (1.01–1.18) per exercise category	Age	Larger effect size for provoked VTE
van Stralen (2008)[17]	The Cardiovascular Health Study (CHS)	Men and women, 65 y and older	171	Dichotomized as active or inactive based on total weekly kilocalories expended on leisure time and household activities ($\geq$or $<$ 500 kcal). Mild, moderate, and strenuous exercise defined as METs $<$4, 4–6, and $>$6, respectively	Yes	11.6 y	HR 1.75 (1.08–2.83) for strenuous compared with no exercise	Age, sex, baseline BMI, and self-reported health	Mild intensity exercise was associated with lower risk, HR 0.75 (0.49–1.16 when compared with no exercise
No association									
Borch (2010)[19]	The Tromsø Study	Men and women, 25–97 y	460	Four categories based on weekly duration of moderate and high intensity PA during leisure time (breathless/sweating)	No	12.5 y	No association between PA and VTE	Age, sex, BMI, diabetes, smoking, and hormone therapy	
Holst (2010)[23]	Copenhagen City Heart Study	Men and women, aged 20 y and older	969	Leisure time PA dichotomized into sedentary or moderately activity $<$4 h/wk, or moderate or intense activity $>$4h/wk. Work-related activity assessed separately based as mostly sitting/standing versus lifting and heavy physical work	No	19.5 y	No association between PA and VTE	Age and calendar time	

Table 1 (*Continued*)

First author (year)	Cohort	Study population	VTE-events	PA assessment[a]	Reassessed PA	Follow-up	Main findings	Confounders	Comments
Kabrhel (2011)[22]	Nurses' Health Study	Women, 30–55 y	268 (PE only)	Five categories based on weekly METs (calculated from hours/week spent in various activities)	No	18 y	No association between PA and VTE		
Lutsey (2010)[20]	Iowa Women's Health Study	Women, 55–69 y	2,137	Three-level summary index based on the frequency of moderate (e.g., golf) and vigorous (e.g., aerobics) PA	No	13 y	No association between PA and VTE in multivariable analyses	Age, education, smoking status, and BMI	Moderate and high intensity PA associated with 16% (HR: 0.84 (0.76–0.93) and 19% (0.81 (0.72–0.90) lower risk of VTE in the age-adjusted model
Tsai (2002)[21]	The Atherosclerosis Risk in Communities (ARIC) Study and The Cardiovascular Health Study (CHS)	Men and women ARIC: 45–64 y CHS: 65 y and older	ARIC: 130 CHS: 85	ARIC: Five-level index based on the Baecke Leisure and Sport Questionnaires CHS: Five categories based on weekly kilocalories expended on leisure time and household activities	No	7.8 y	No association between PA and VTE	Age, race, and sex	Analyses were done separately for the two studies due to different assessment of physical activity

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents; PA, physical activity; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.
[a]All studies are based on self-reported physical activity.
[b]Not analyzed as a time-varying covariate.
[c]Adjusted for age, coronary heart disease, hypertension, menopausal status, multivitamin use, use of nonaspirin nonsteroidal anti-inflammatory drugs, parity, race, rheumatologically disease, spouse's highest educational attainment, smoking status, pack-years, warfarin use, BMI, total energy intake, physical activity, and dietary pattern.

interpretation of epidemiological studies on physical activity. In general, studies with a prospective design have important advantages compared with retrospective (e.g., case–control) studies in that there is a clear temporal sequence between exposure and outcome, enhanced generalization of findings, and unbiased exposure information. Particularly, recall bias is highly relevant in studies with a retrospective assessment strategy. In this context, it is striking that all studies with retrospective assessment of physical activity have reported a lower risk of VTE with higher amounts of physical activity,[32–34] whereas findings from prospective cohort studies have been less consistent.[16,18,19] It may be that subjects with an acute VTE event recall or describe their activity habits differently compared with healthy controls, which introduces a form of differential misclassification resulting in biased risk estimates in retrospective studies.[35]

Accurate assessment of the variables under study is critical in all research. Physical activity is a complex behavior that lacks an operational definition and a standardized assessment method.[36,37] This is reflected in the range of available instruments, and the choice largely depends on the information of interest (intensity, frequency, total energy expenditure, domain, etc.), study size, available resources, and the required level of precision. Various self-report instruments, such as questionnaires, are most common in large observational studies.[38] However, these vary widely in the level of detail, time perspective, and what dimensions (mode, frequency, duration, intensity) and domains (occupational, domestic, transport, leisure) that are in focus.[36] Self-administered questionnaires have valuable strengths in terms of cost-effectiveness, feasibility, and ability to discriminate between inactive and active individuals. However, compared with objective assessment methods, they are less accurate, and prone to error and bias due to recall and social desirability.[36]

The wide selection of available instruments is reflected in studies on the association between physical activity and the risk of VTE. The focus ranges from total weekly amount or frequency of physical activity of various intensities[15,16,18,19] via crude dichotomization[23] to estimation of caloric expenditure[17,21] and global assessment batteries.[14] Furthermore, the dimensions and time perspectives, if specified, differ between studies, although the majority have displayed an interest in leisure-time activity with emphasis on frequency and intensity rather than the type of activity. Importantly, the different dimensions of physical activity relate to distinct physiological responses, for example, high-intensity aerobic exercise relates to maximal oxygen uptake, while light-intensity activity is more strongly correlated with total energy expenditure.[39–41] Knowledge and validation of the actual physiological exposure is critical, as it influences the interpretation of study findings and dictates the translation of findings into public health recommendations.[37]

A way to indirectly validate information of exposure (e.g., physical activity) gathered from self-administered questionnaires is to explore the effect on another outcome with a well-established association with the exposure variable. In the Tromsø study, we have investigated the association between weekly physical activity during leisure time and the risk of incident myocardial infarction (MI) and VTE within the same cohort recruited from the general population ($n = 26{,}215$). The study design and population have been described in detail elsewhere.[19,42] As expected, we found an inverse association between physical activity and MI risk of a magnitude of 20 to 29% that displayed a dose–response relationship across categories of increasing weekly amount of physical activity (p for trend < 0.001, ►**Table 2**). In contrast, there was no association between physical activity and the risk of VTE (►**Table 2**). Our finding of an inverse association between physical activity and MI risk corroborates previous research and supports the validity of our physical activity questionnaire.[9] Although we found no association between physical activity and VTE risk in this study design, there could still be a small effect that is masked by fluctuations in activity habits and/or residual confounding variables (e.g., time spent in sedentary behavior that is independent of the overall amount of physical activity).

In longitudinal studies, a challenge emerges due to the potential fluctuating nature of physical activity during follow-up.[43,44] If not accounted for, this may lead to regression dilution bias and possibly an underestimation of the true association.[45] For instance, the risk of premature mortality according to physical inactivity was reported to increase 24 to 59% when change in behavior during follow-up was accounted for, as compared with analyses based on baseline data.[43] Up to now, we are aware of only two studies[14,17] investigating the association between physical activity and risk of VTE that have modeled physical activity as a time-varying covariate. Moreover, the studies that reported an association typically had shorter follow-up compared with the studies reporting null findings (►**Table 1**). Although the association between physical activity and MI remained during a 19-year follow-up in the Tromsø study (►**Table 2**), it is likely underestimated due to regression dilution. Thus, a smaller effect size of physical activity on VTE risk could still be present but not detected in a traditional cohort design with single measurements and long-term follow-up.

Confounding variables may strengthen or weaken an association, and strategies to minimize such confounding variables include stratification or multivariable-adjusted analysis.[46] In the context of physical activity and VTE, the influence of weight status is of particular interest, as physical activity is a key component in weight maintenance,[47,48] and obesity and weight gain are strong predictors of VTE.[49–51] Hence, obesity may act as a confounder, but is likely also in the causal pathway between physical activity and VTE. Most studies statistically adjust for the effect of BMI, which typically attenuate the risk estimates for the association between physical activity and VTE by 3 to 24%.[14,16,20] However, due to the potential interrelationship, such analyses may be over-adjusted and the true association underestimated.

The inconsistent findings reported up to now on the association between physical activity and risk of VTE may partly be due to aspects related to study design, exposure assessment strategy, and data handling. Future studies that account for the fluctuating nature in human behavior and

Table 2 Incidence rates and hazard ratios with 95% CIs for the risk of MI and VTE by physical activity status (the Tromsø study, 1994–2013)

	Myocardial infarction				VTE			
Physical activity status	MI events	IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]	VTE events	IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Inactive[d]	621	7.25 (6.70–7.84)	1.00	1.00	195	2.19 (1.90–2.51)	1.00	1.00
Light PA 1–3 h/wk	478	4.70 (4.30–5.14)	0.77 (0.68–0.87)	0.80 (0.71–0.91)	196	1.86 (1.62–2.14)	0.98 (0.81–1.20)	1.03 (0.84–1.26)
Light PA >3 h/wk	509	5.93 (5.44–6.47)	0.73 (0.65–0.82)	0.78 (0.69–0.88)	201	2.25 (1.96–2.58)	0.94 (0.77–1.15)	1.02 (0.84–1.25)
Hard PA 1–3 h/wk	255	3.03 (2.68–3.41)	0.63 (0.55–0.74)	0.71 (0.62–0.83)	98	1.14 (0.94–1.39)	0.84 (0.66–1.08)	0.92 (0.72–1.19)
Hard PA >3 h/wk	160	3.72 (3.18–4.34)	0.69 (0.58–0.82)	0.78 (0.65–0.93)	64	1.46 (1.14–1.86)	1.02 (0.77–1.36)	1.11 (0.83–1.49)
p for trend			<0.001	<0.001			0.432	0.928

Abbreviations: CIs, confidence intervals; HR, hazard ratio; MI, myocardial infarction; PA, physical activity; light PA, not sweating or out of breath; hard PA, sweating or out of breath; VTE, venous thromboembolism.
[a]Crude incidence rates per 1,000 person-years.
[b]Adjusted for age (as time scale) and sex.
[c]Adjusted for age (as time scale), sex, body mass index, and smoking.
[d]No or less than 1 h of physical activity per week.

apply well-defined, preferably objective, assessment strategies of both physical activity (e.g., accelerometry) and sedentary behavior are needed. The role of physical fitness, such as cardiorespiratory endurance and muscle strength, should also be further explored in this context. This may not only clarify the nature of the potential association between physical activity and the risk of VTE but also provide more valid effect sizes and generate hypotheses regarding potential mechanisms.

Plausible Mechanisms for an Association between Physical Activity and Venous Thromboembolism

Under normal physiological conditions, the hemostatic system is regulated through a delicate balance between pro- and anticoagulant activity to maintain blood fluidity. In contrast, thrombosis refers to pathological clot formation that is not required for hemostatic function.[52] The framework for understanding the pathophysiology of thrombosis was proposed by Virchow in 1856, who suggested that thrombus formation results from changes in the vessel wall, the blood flow, and the blood composition.[53] There are several potential mechanisms for an association between physical activity and VTE, and all relate to the three aspects of Virchow's triad.

Blood Flow

Physical activity increases energy turnover and requires rapid cardiovascular responses with increased blood flow to the working muscles. Cardiac output, the amount blood pumped by the heart every minute, increases four- to sevenfold from rest to maximal exercise. This profound rise in blood flow results from an increase in heart rate and stroke volume, with the latter largely depending on enhanced ventricular filling (preload) and myocardial contractility. The skeletal muscle pump plays a vital role in emptying the veins of the lower extremities, where blood pools due to gravity, into the central circulation.[54,55] The blood flow profile is also influenced, and exercise has been shown to increase anterograde blood flow and decrease oscillatory shear rate in arteries.[56,57] It follows that during activity, the blood flow responses potentially create an antithrombotic environment.

Research on whether regular physical activity or exercise influences the blood flow profile during rest is limited. However, increased venous flow has been recorded up to 30 minutes after exercise cessation.[58] Moreover, in subjects with venous insufficiency, a 6-month exercise program with focus on calf muscle strength improved the calf muscle pump function.[59] In addition, higher resting blood flow in femoral arteries has been reported in trained compared with untrained individuals.[60]

Vessel Wall

Although venous blood clots most often form in the presence of an intact endothelium,[61,62] disruption of endothelial integrity potently activates the hemostatic system.[63] Participation in high-impact and high-intensity activities may increase the risk of injury,[64,65] and thus partly explain the increased thrombotic risk associated with physical activity reported in some studies.[17,66]

The endothelium is a multifunctional organ that exerts an expanding amount of important functions. In addition to regulating vascular tone and creating a physical barrier between blood and tissues, it also influences the hemostatic balance.[67,68] Diverging with time and location, the endothelium expresses anticoagulant/antithrombotic factors, such as thrombomodulin (TM), tissue-type plasminogen activator

(t-PA), and tissue factor pathway inhibitor (TFPI), as well as procoagulant/prothrombotic factors, such as tissue factor, thrombin receptors, von Willebrand factor (VWF), and plasminogen activator inhibitor (PAI-1).[68] The exercise-related responses in the expression of these markers are discussed in the sections on "Blood Composition" (later). The vasoactive hormones nitric oxide (NO) and prostacyclin that are released from the endothelium may also influence the hemostatic balance by regulating flow conditions and modulating platelet activity.[69,70] Although the endothelium normally displays an antithrombotic phenotype, a hallmark of endothelial dysfunction is an inability to release and respond to NO.[67,70] Endothelial dysfunction exerts an important role in the pathophysiology of atherosclerosis,[71] and impaired endothelial function has also been observed in patients with VTE.[72] Enhanced endothelial function, assessed by flow-mediated dilation (FMD), has been observed after a period of exercise in both healthy individuals and in patients with established endothelial dysfunction, and is thought to be mediated by increased bioavailability of NO.[73,74]

Hemorheology

Exercise also alters hemorheology, that is, the flow characteristics of the blood, as reviewed by El-Sayed et al.[75] Whole blood viscosity is largely determined by hematocrit and the rheological properties of the plasma and cellular components, and depends on shear rate.[76] Moreover, the relative influence of hematocrit on blood viscosity is higher under conditions with low shear rate.[77] The latter particularly applies to the venous system and may mediate the association between high hematocrit and an increased risk of VTE.[78] A transient increase in whole blood viscosity is typically observed following endurance exercise.[75,79,80] This is potentially due to increased hemoconcentration resulting from loss of total body water through perspiration and transition of fluid from the vasculature into the interstitial space, with subsequent increases in hematocrit and plasma viscosity.[75,79,80]

There is a paucity of data on the long-term effects of regular physical activity and exercise on the rheological properties of the blood.[75] An increase in blood volume is a well-documented response to endurance training.[54] In the early phases of training, this is mainly due to plasma volume expansion without a concomitant increase in red blood cell mass.[54,81,82] Further, inverse associations have been reported between both physical work capacity[83] and habitual physical activity,[84] and hematocrit and blood and plasma viscosity. Although not all studies have demonstrated any difference in hemorheologic properties between trained and untrained individuals,[79] it has been suggested that endurance training probably is associated with a reduction in blood viscosity.[75] Thus, it appears that the short-term hemorheologic responses to exercise may result in an increased thrombotic risk, while the long-term adaptations potentially facilitates an antithrombotic milieu.

Blood Composition—Short-Term Effects

Physical activity is recognized as a potent modulator of the hemostatic system.[85–87] The most consistently reported short-term responses are summarized in ►**Table 3**. Several studies have shown that platelet count transiently increases in response to exercise in an intensity-dependent manner.[88–92] The rise is beyond what is explained by the change in plasma volume,[91] and returns to baseline values within 2 hours after termination of exercise.[91,92] In contrast, data on the effects of exercise on platelet function are conflicting, potentially due to large methodological variations.[86,93] However, it has been suggested that high intensity and maximal exercise may induce platelet activation as shown by increased plasma concentrations of β-thromboglobulin (β-TG) and platelet factor 4 (PF4).[88,91]

Exercise also transiently increases the coagulation potential as demonstrated by a shortening in clotting time and activated partial thromboplastin time (aPTT), while prothrombin time (PT) is negligibly affected.[94–98] A shortening in aPTT has been observed after both endurance- and resistance-type exercises[94,99] appear to be independent of exercise intensity,[91,95] and remain shortened at least 1 hour after termination of exercise.[91,97] The shortened clotting time is probably a result of a concomitant rise in coagulation factor VIII (FVIII) complex activity. Both components of the FVIII complex (FVIII and VWF) have been reported to increase in response to exercise in an intensity-dependent manner and may persist above resting levels for up to 10 hours after exercise.[94,97,100–103] The effect on other coagulation factors including fibrinogen is less certain and probably less pronounced.[86,103–105] Moreover, intensity-dependent increases in markers of thrombin generation (prothrombin fragment 1 + 2 (F1 + 2) and thrombin–antithrombin [TAT] complex) have also been reported after exercise.[94,99,106–108]

Limited data exist on the acute effects of exercise on the anticoagulant pathways, such as antithrombin, protein C, and TFPI. However, while no effect was observed on the levels of protein C and antithrombin in one study,[109] antithrombin was reported to decrease after exercise when adjusted for changes in plasma volume in another study.[98] Moreover, a significant rise in TFPI has been reported immediately after and up to 10 hours following exercise with maximal effort, suggesting a role for TFPI in suppressing coagulation activation during and after extensive exercise.[108,110]

Exercise also transiently influences the fibrinolytic system. Specifically, enhanced fibrinolytic potential has been observed after exercise, assessed as shortened blood clot lysis time, and increased levels and activity of t-PA.[91,94,99,101,111] The rise in t-PA is dependent on exercise intensity, and potentially results from endothelial activation due to shear stress.[86] Moreover, decreased levels and activity of PAI-1 have also been reported after exercise, further supporting a greater fibrinolytic potential.[94,99,111,112] Notably, the response in t-PA appears to be highly transient, and returns to baseline levels earlier than the procoagulant markers.[97,101,113,114] In addition, a secondary inhibition of fibrinolysis has been observed 2 to 4 hours after strenuous exercise.[101] This imbalance may contribute to the increased cardiovascular risk observed shortly after strenuous exercise.[97,114]

Table 3 Short-term hemostatic responses to exercise

Parameter	Effect	Magnitude of effect	Comment	Reference
Platelets				
Count	Increased	7–29%	Intensity dependent Effect observed after both endurance and resistance exercise	88–92
Activation/ reactivity	Uncertain/increased Unchanged/increased	β-TG: -13–155% PF4: -1–122%	Intensity dependent Intensity dependent	88,91 88
Coagulation				
aPTT	Shortened	5–13%	Independent of intensity Effect observed after both endurance and resistance exercise	91,94,95,97–99
PT	Unchanged	n/a		94,95
F1 + 2	Increased	5–88%	Intensity dependent Effect observed after both endurance and resistance exercise	94,99,106,107
TAT	Unchanged/increased	0–173%	Intensity dependent Effect observed after both endurance and resistance exercise	94,99,106,108
FVIII activity	Increased	34–400%	Intensity dependent Effect observed after both endurance and resistance exercise	94,97,100,102,103
VWF	Increased	96–200%	Dependent on intensity	100,101
Fibrinolysis				
t-PA activity	Increased	119–1,525%	Intensity dependent Effect observed after both endurance and resistance exercise	94,99,111,112
PAI-1 activity	Decreased	−19 to −83%	Probably not or less dependent on intensity Effect observed after both endurance and resistance exercise	94,99,111,112

Abbreviations: aPTT, activated partial thromboplastin time; F1 + 2, prothrombin fragment 1 + 2; FVIII, coagulation factor VIII; PAI-1, plasminogen activator inhibitor-1; PF4, platelet factor 4; PT, prothrombin time; TAT, thrombin–antithrombin complex; t-PA, tissue plasminogen activator; VWF, von Willebrand factor; β-TG, β-thromboglobulin.

Blood Composition—Long-Term Adaptations

The long-term hemostatic adaptations to regular physical activity and exercise are summarized in ►**Table 4**. Aerobic exercise interventions of 8 to 12 weeks of duration have shown to decrease platelet activity during rest.[115–118] Furthermore, the platelet activation commonly observed after exercise appears to be attenuated after a period of aerobic exercise[88,116] and in trained compared with untrained subjects.[119] This is potentially mediated by a platelet-inhibiting effect of NO and prostacyclin, and associated with enhanced endothelial function.[69,115]

In contrast, markers of coagulation and thrombin generation during rest, including aPTT, PT, TAT, and F1 + 2, appear not to be influenced by the amount of habitual physical activity[98,99,120] or after 12 weeks of aerobic exercise.[121,122] However, the literature is not entirely consistent, with one study reporting a prolongation in aPTT during rest after 12 weeks of aerobic exercise,[105] while a small reduction in basal F1 + 2 was reported in older adults after 6 months of aerobic exercise.[123] Furthermore, while habitual physical activity was inversely associated with resting fibrinogen, FVIII, and VWF in a cross-sectional study of men,[84] these observations have not been confirmed in longitudinal studies with aerobic exercise interventions.[105,121,124] Accordingly, the plasma levels of FVIII and VWF under resting conditions in endurance-trained athletes do not appear to differ from less active controls.[125]

Few studies have investigated whether training status influences the short-term coagulation response to exercise.

Table 4 Long-term adaptations to regular physical activity and exercise on resting hemostasis

Parameter	Effect	Magnitude of effect	Comment	Reference
Platelets				
Activation/ reactivity	Reduced Reduced Lower	Numbers not reported Basal CD62P[a]: 42.7% Numbers not reported	Pre- vs. postintervention Pre- vs. postintervention Trained vs. untrained	115,116 118 118
Coagulation				
aPTT	Prolonged Unchanged	10.3% n/a	Pre- vs. postintervention Trained vs. Untrained and pre- vs. postintervention	105 98,99,121,122
PT	Unchanged	n/a	Trained vs. untrained	98
F1 + 2	Unchanged Decreased	n/a 4.8%	Trained vs. untrained and pre- vs. postintervention Pre- vs. postintervention	99,120,122 123
TAT	Unchanged	n/a	Trained vs. untrained	99,120
FVIII activity	Decreased Unchanged	5.6% n/a	Trained vs. untrained Pre- vs. postintervention	84 105,121,124
VWF	Decreased Unchanged	7.2% n/a	Trained vs. untrained Trained vs. untrained and pre- vs. postintervention	84 122,125
Fibrinolysis				
t-PA activity	Increased Unchanged	39% n/a	Pre- vs. postintervention Trained vs. untrained and pre- vs. postintervention	126 105,112,122
PAI-1 activity	Decreased Unchanged	58% n/a	Trained vs. untrained and pre- vs. postintervention Pre- vs. postintervention	112,126 105,124

Abbreviations: aPTT, activated partial thromboplastin time; F1 + 2, prothrombin fragment 1 + 2; FVIII, coagulation factor VIII; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; TAT, thrombin–antithrombin complex; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.
[a]Marker of platelet activation.

However, it has been suggested that endurance-trained athletes display a diminished response, as demonstrated by a lower increase in F1 + 2, compared with less trained controls.[120] Likewise, a less pronounced shortening of aPTT and attenuated increase in F1 + 2 was reported after a 12-week aerobic exercise intervention.[105] In contrast, one study reported an augmented response in F1 + 2, and a more pronounced shortening of aPTT, in response to maximal exercise following 12 weeks of aerobic exercise.[122] However, the transient increase in FVIII activity evoked by exercise appears to be unaltered following an aerobic exercise intervention,[105,121] although an augmented response after training has also been suggested.[122,124]

An increase in t-PA activity and a decrease in PAI-1 activity during rest were reported after 6 months of aerobic exercise in elderly, while no such repose was observed in young subjects.[126] In contrast, two other studies did not observe any changes in resting activity of t-PA or PAI-1 after 12 weeks of aerobic exercise.[105,122] Further, in a cross-sectional study, resting t-PA activity was similar in active and inactive men, while PAI-1 activity was higher among the inactive.[112] Data on whether training status influences the fibrinolytic response to exercise are sparse. However, based on the available evidence, it can be suggested that trained individuals display an amplified fibrinolytic potential in response to maximal intensity exercise,[112,122,127] but probably not to submaximal exercise.[105,122]

In summary, although exercise evokes significant transient responses in both the coagulation and fibrinolytic systems, it remains unclear whether this results in a net hypercoagulable state.[86,128] Nevertheless, the more transient nature of the fibrinolytic response may induce a disturbed balance and contribute to the increased cardiovascular risk observed shortly after strenuous exercise.[97,114] There are inconsistent findings on the long-term adaptations to physical activity and exercise.[129] However, the available evidence implies that training status only moderately influences hemostasis assessed under resting conditions, while the fibrinolytic response to maximal intensity exercise may be amplified in trained subjects. Importantly, the available studies display large methodological variance related to exercise-testing protocols, training interventions, study populations, and analytical methods, which impedes firm conclusions on this topic.

Consequences of Venous Thromboembolism: Is There a Role for Physical Activity?

In addition to thrombus extension and embolization, potential complications following an acute VTE event include morbidity directly or indirectly related to the thrombus, recurrent disease, and death.[130,131] The 1-year all-cause mortality after VTE is reported to be 22 to 24%,[132–134] and in survivors the 1- and 5-year recurrence risks are 13 to 19% and 19 to 29%, respectively.[132,135,136]

To our knowledge, so far only one study has investigated the association between physical activity and the risk of VTE recurrence. In a follow-up arm of the MEGA study,[29] Flinterman et al followed almost 4,000 patients with incident VTE over a period of 5 years. They reported that individuals with a sedentary lifestyle prior to their incident VTE had an increased risk of recurrence that was more prominent in women (hazard ratio [HR]: 1.5; 95% confidence interval [CI]: 1.1–2.0) than in men (HR: 1.1; 95% CI: 0.9–1.4).[29] It is currently not known whether physical activity after the incident VTE influences the risk of recurrence. Nevertheless, a sedentary lifestyle will increase the risk of other metabolic and cardiovascular diseases, and premature mortality.[8,10,11]

Postthrombotic syndrome occurs in 20 to 50% of patients with lower limb deep vein thrombosis (DVT), and manifests with pain, swelling, and heaviness of the affected extremity.[131,137,138] The condition is associated with impaired quality of life and significant health care costs.[139,140] PTS most often occurs in patients with recurrent ipsilateral DVT, and predisposing factors include older age, insufficient anticoagulant treatment, and impaired thrombus resolution.[131,141,142] As there is currently no effective treatment strategy for PTS, prevention is pivotal.[142] A potential preventive role for physical activity has been suggested. Specifically, a small intervention study[143] reported that early mobilization, as compared with bed rest, was associated with a lower 2-year incidence and severity of PTS symptoms in patients with acute DVT. In contrast, another study[144] did not find any significant association between self-reported physical activity 1 month after DVT and risk of developing PTS during the subsequent 2 years. Interestingly, a randomized controlled trial investigating the effect of supervised exercise on the risk of PTS is currently underway (NCT02148029). There is limited data on the effect of physical activity in the treatment of PTS. However, improved calf muscle pump function was reported after a 6-month exercise program in patients with chronic venous insufficiency (50% with a history of DVT).[59] In addition, a pilot study in patients with established PTS reported that a 6-month exercise program improved quality of life, but the small beneficial effect on PTS symptoms did not reach statistical significance.[145]

Less prevalent but more debilitating, CTEPH, characterized by dyspnea, physical impairment, and impaired quality of life, affects 0.5 to 4% of patients with PE.[146,147] The exact pathophysiology behind CTEPH is unclear, but is potentially driven by impaired thrombus resolution with subsequent development of fibrotic occlusions and vascular remodeling.[131,148] Previous PE, larger perfusion defects, lupus anticoagulant, antiphospholipid antibodies, and elevated FVIII levels are reported to be associated with the development of CTEPH.[148] To our knowledge, no study has so far investigated the association between physical activity and the risk of CTEPH in patients with PE. However, exercise-based rehabilitation programs have shown promising effects on exercise capacity and quality of life in patients with pulmonary hypertension including CTEPH, although we are not aware of any studies restricted to patients with CTEPH only.[149,150]

Studies indicate that early mobilization after an acute VTE does not increase the risk of disease progression or adverse events.[151,152] Moreover, one study on selected VTE patients reported that maximal exercise testing and structured aerobic exercise early after acute VTE (≥6 weeks) was safe, feasible, and efficient.[153] However, research on whether physical activity influences the risk and prognosis of VTE-related complications is limited.

Conclusion

Despite a considerable amount of research, the association between physical activity and risk of incident VTE has yet to be thoroughly established. As summarized in the present review, the available evidence is inclined toward a beneficial effect of physical activity on the risk of incident VTE, but not in a dose-dependent manner. There is, however, considerable methodological variance between the published studies, which largely precludes head-to-head comparisons. Future studies utilizing objective assessment strategies and accounting for fluctuations in behavior may aid to reveal the true association.

The potential role of physical activity in the secondary prevention of VTE and in relation to PTS and CTEPH has to date been investigated with a fragmented approach. Consequently, there is a need to explore the necessity and potential benefits of structured rehabilitation programs, equivalent to that in cardiac rehabilitation, in the VTE setting.

Conflict of Interest
None.

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PAPER II

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ORIGINAL ARTICLE

Repeated assessments of physical activity and risk of incident venous thromboembolism

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Essentials

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

Summary. *Background:* Whether physical activity influences the risk of incident venous thromboembolism (VTE) remains controversial, potentially because of 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 (1994–1995, 2001–2002, and 2007–2008) were included and categorized on the basis of weekly physical activity. Incident VTE was registered until 31 December 2016. Hazard ratios (HRs) were calculated by the use of time-varying Cox regression models. The Aalen additive hazard model was used to quantify the total, direct and indirect effects of physical activity. *Results:* There were 531 incident VTEs during follow-up. Physical activity (≥ 1 per week) was associated with a lower risk of VTE (HR 0.77, 95% confidence interval [CI] 0.64–0.92) than being inactive. The effect was most pronounced for those aged ≥ 65 years (HR 0.70, 95% CI 0.55–0.88) and for provoked events (HR 0.66, 95% CI 0.50–0.89). The differences in absolute risk between active and inactive individuals were − 0.42 (95% CI − 0.73 to − 0.14) and − 1.59 (95% CI − 2.74 to − 0.52) events annually per 1000 individuals in the total and elderly populations, respectively. A moderate proportion of the association (14–36%) was mediated via BMI. *Conclusion:* Our findings suggest that regular physical activity is associated with a lower risk of VTE, particularly in the 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.

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Introduction

Venous thromboembolism (VTE) affects 1–2 per 1000 individuals annually, and represents a significant public health burden, owing 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 of VTE has remained stable or increased slightly in the period 1990 to 2010 [2,7]. Moreover, with a growing prevalence of important risk factors, such as cancer, obesity, and an aging population, the total number of 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 than 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 for 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 VTE risk [18,21], particularly in the elderly [22]. However, findings from several large cohort studies suggest that physical activity does not influence VTE risk 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]. Owing to the potential fluctuating nature of physical activity, the risk estimates in these studies may be underestimations because of regression dilution [28,29]. To date, we are aware of only two studies, restricted to middle-aged [16] and elderly [22] people, which have accounted for changes in activity habits during follow-up. Furthermore, 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 to be 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 (1994–1995), fifth (2001–2002) and sixth (2007–2008) 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 25–89 years at inclusion. Individuals who did not consent to medical research (n = 181), who were not officially registered as inhabitants of the Tromsø municipality at baseline (n = 23), with a prebaseline 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 that 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 from 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 h', '1–2 h', or '≥ 3 h'. The reliability of the question on hard physical activity has been shown to be moderate, and it is reasonably well correlated with data from motion sensors, maximal oxygen uptake ($V\mathrm{O}_{2\mathrm{max}}$), and the International Physical Activity Questionnaire (IPAQ) [33]. The question on light physical activity has been 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 min', '15–29 min', '30–60 min', or '> 1 h'). The reliability of the questionnaire has been reported to be high, and it is well correlated with objective measures of physical activity, IPAQ, and $V\mathrm{O}_{2\mathrm{max}}$ [34]. The 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 to be 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 answer the intensity question, but provided information on frequency and duration, were placed in the lowest intensity-category.

We also constructed a common five-level variable with one inactive group that comprised participants reporting 'no activity' or '< 1 h per week', and four active groups: '1–3 h per week of light activity', '> 3 h per week of light activity', 1–3 h per week of hard activity', and '> 3 h per 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, whereby the four active groups were merged (i.e. '≥ 1 h per week') and compared with the inactive group (i.e. 'no activity' or '< 1 h per week').

Identification and adjudication of VTE

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 (1994–1995, 2001–2002, or 2007–2008) to 31 December 2016. The 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 the presence of signs and symptoms of pulmonary embolism (PE) or deep vein thrombosis (DVT) combined with objective confirmation by radiological procedures that resulted in treatment initiation (unless contraindications were specified). The process of case identification and adjudication has been previously 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 of ≥ 3 days, being confined to a wheelchair, or long-distance travel for ≥ 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 enrollment to the date of incident VTE, death, migration or 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 (1994/1995–2002) or Tromsø 5 (2001/2002–2008), whereas follow-up for Tromsø 6 (2007/2008) ended on 31 December 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 for PE and DVT, were estimated by the use of time-varying Cox proportional hazards regression models with the least active group ('no activity' or '> 1 h per 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 the time scale, with the age at

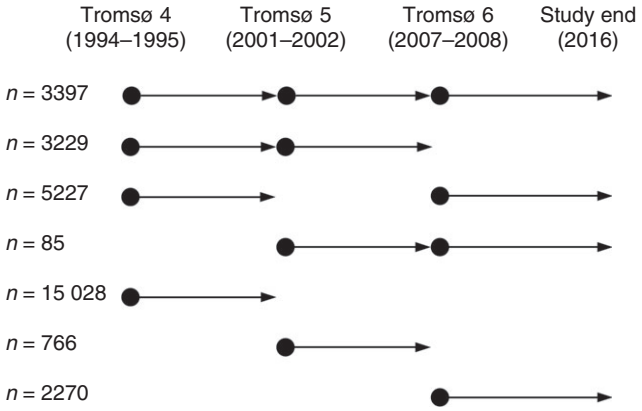

Fig. 1. Overview of study participation (dots) and observation periods (arrows). In total, 30 002 individuals were included in the study. Of these, 18 064 participated in one survey, 8541 participated in two surveys, and 3397 participated in three surveys.

enrollment being defined as the entry time, and the age at VTE or censoring being defined as the 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 years 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 by use of 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 use of the formula $([IR_p - IR_a]/[IR_p]) \times 100\%$ [13]. Calculations were performed 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 the basis of the Aalen additive hazard model [38]. This method provides an estimate of the absolute difference in risk per unit time with the 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

The 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 of 6.8 ± 1.6 years), there were 531 incident VTE events, yielding a crude IR of 1.56 per 1000 person-years (95% CI 1.43–1.69). The baseline characteristics across categories of physical activity are shown in Table 1. Although the proportion of inactive individuals was similar in men and women, active women were more likely to engage in light physical activity, and active men were more likely to engage in in hard physical activity. Also, 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 than those in the other categories.

The characteristics of the VTE events are shown in Table 2. The mean age at the time of incident VTE was 68 ± 12 years. The most common clinical presentation was DVT, accounting for 59% of the cases; the remaining 41% presented as PE with or without concurrent DVT. Furthermore, 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-adjusted and sex-adjusted model, there was a significant trend of a lower VTE risk 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 h per week' to '1–3 h per week of light activity'), and the CIs of the risk estimates for the remaining categories

Table 1 Baseline characteristics of participants (n = 30 002) across categories of weekly physical activity (PA); 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), mean (SD)	50 (16)	47 (14)	50 (16)	42 (12)	41 (12)
Sex (women), *n* (%)	52.3 (3787)	58.5 (4181)	60.5 (3733)	47.1 (2974)	34.6 (1087)
BMI (kg m^{-2}), mean (SD)	26.0 (4.4)	25.4 (4.0)	25.1 (3.8)	24.9 (3.5)	24.7 (3.2)
Triglycerides (mmol L^{-1}), mean (SD)	1.71 (1.15)	1.57 (1.04)	1.50 (0.97)	1.45 (0.99)	1.44 (1.02)
Total cholesterol (mmol L^{-1}), mean (SD)	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}), mean (SD)	1.45 (0.40)	1.50 (0.41)	1.54 (0.42)	1.49 (0.40)	1.50 (0.41)
Systolic blood pressure (mmHg), mean (SD)	136 (23)	134 (20)	136 (22)	130 (18)	131 (17)
Smoking, *n* (%)	40.1 (2899)	37.6 (2685)	36.6 (2258)	30.4 (1916)	29.3 (920)
Higher education§, *n* (%)	23.6 (1696)	29.1 (2074)	28.8 (1765)	45.4 (2964)	41.3 (1292)
History of CVD, *n* (%)	9.6 (692)	6.2 (440)	8.0 (491)	2.7 (171)	2.7 (85)
History of cancer, *n* (%)	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); SD, standard deviation. *Less than 1 h of PA per week. †Activity at an intensity not causing breathlessness and sweating. ‡Activity at an intensity causing breathlessness and sweating. §Fifteen or more years of education (corresponding to 3 years in university or academy).

Table 2 Characteristics of venous thromboembolism (VTE) events (n = 531); the Tromsø Study (1994–2016)

	% (n)
Age (years), mean (SD)	68 (12)
Sex (women), n (%)	50.1 (266)
Clinical characteristics, n (%)	
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. *No provoking factors at the time of diagnosis. †One patient may have multiple provoking factors. ‡Bedrest of ≥ 3 days, long-distance travel for ≥ 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 years. **Other diseases within the previous year (myocardial infarction, ischemic stroke heart failure, inflammatory bowel disease, or myeloproliferative disorders).

largely overlapped. The risk estimates were attenuated after adjustment for BMI (16% lower risk), whereas adjustment for history of CVD and cancer did not further influence the risk estimates. Analyses stratified by age at baseline (< 65 years or ≥ 65 years) revealed that the association was most pronounced in those aged ≥ 65 years. Here, there was a significant trend of a lower VTE risk across categories of physical activity (P = 0.004), which remained statistically significant after adjustment 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, and there were overlapping CIs 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 a 23% lower VTE risk (HR 0.77, 95% CI 0.61–0.92) than inactive individuals. The risk estimate was attenuated after adjustment for BMI (16% lower risk), whereas adjustment for history of CVD and cancer did not further modify the association. In those aged ≥ 65 years, physical activity was associated with a 30% lower VTE risk (HR 0.70, 95% CI 0.55–0.88). The association was attenuated, but still significant, after adjustment for BMI and history of CVD and cancer (25% and 24% lower risks, respectively). In those aged < 65 years, physical activity was associated with a 15% lower risk, but the risk estimate was not statistically significant (HR 0.85, 95% CI 0.64–1.13). The proportions of VTE events attributable to physical inactivity were 12.2%, 6.0% and 12.5% for the total study population, for those aged < 65 years, and for those aged ≥ 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 being observed in those aged ≥ 65 years and in relation to provoked events. Elderly individuals who were physically active had a 34% lower risk of provoked VTE (HR 0.66, 95% CI 0.50–0.89) than those who were inactive, and the association remained significant after adjustment 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 aged ≥ 65 years (HR 0.76, 95% CI 0.52–1.13). We also performed analyses separately for PE and DVT (Table 6; Table S3). In those aged ≥ 65 years, physical activity was associated with lower risks of PE (HR 0.69, 95% CI 0.48–0.98) and DVT (HR 0.70, 95% CI 0.52–0.96), but this association was attenuated after adjustment for BMI. In those aged < 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 in relation to 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 individuals was – 0.42 (95% CI − 0.73 to − 0.14) per 1000 persons at risk annually, of which 23% (95% CI 11–68) was attributable to BMI. The corresponding differences in risks in those aged < 65 years and ≥ 65 years were − 0.20 (95% CI − 0.42 to − 0.07) and − 1.59 (95% CI − 2.74 to − 0.52) per 1000 persons at risk annually, respectively. A larger proportion of the effect was mediated via BMI in those aged < 65 years (36%, 95% CI 15–90) than in those aged ≥ 65 years (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 VTE risk has been the focus of several investigations, and different results have been reported. Our findings, along with the 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,

Table 3 Age-stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for total venous thromboembolism (VTE) by categories of weekly physical activity (PA); 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	0.834	0.852
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

*Per 1000 person-years. †Adjusted for age (as time scale) and sex. ‡Model 1 + body mass index. §Model 2 + history of cardiovascular disease and cancer.

Table 4 Total and age-stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for total venous thromboembolism (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)

*Per 1000 person-years. †Adjusted for age (as time scale) and sex. ‡Model 1 + body mass index. §Model 2 + history of cardiovascular disease and cancer. ¶Less than 1 h per week of physical activity. **One or more hours per week of physical activity.

> 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 a 19–31% lower VTE risk than those in category 1 [16]. Likewise, in the REGARDS Study, participation in physical activity one to three times and four or more times per week was associated with 30% and 41% lower VTE risk, 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 a 4–18% lower VTE risk than 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 an 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,

Table 5 Overall and age-stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for unprovoked and provoked venous thromboembolism (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)

*Per 1000 person-years. †Adjusted for age (as time scale) and sex. ‡Model 1 + body mass index. §Model 2 + history of cardiovascular disease and cancer. ¶Less than 1 h per week of physical activity. **One or more hours per week of physical activity.

Table 6 Overall and age-stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for pulmonary embolism (PE) and deep vein thrombosis (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)§
PE						
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 (1.81–3.14)	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)
DVT						
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)

*Per 1000 person-years. †Adjusted for age (as time scale) and sex. ‡Model 1 + body mass index. §Model 2 + history of cardiovascular disease and cancer. ¶Less than 1 h per week of physical activity. **One or more hours per week of physical activity.

in addition to increased power, explain why the present findings differ from those in 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 is also in line 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 VTE risk [18,22]. Specifically, in the Cardiovascular Health

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

	Direct effect (95% CI) × 10^{-3}*†	Indirect effect (95% CI) × 10^{-3}*†	Total effect (95% CI) × 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 (0.11–0.68)
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 (0.15–0.90)
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 (0.05–0.48)

CI, confidence interval. *Per year. †Adjusted for age (as time scale) and sex. ‡One or more hours per week of physical activity. §Less than 1 h per week of physical activity.

Study (CHS), a cohort of adults aged ≥ 65 years, participation in strenuous physical activity was associated with a 75% higher VTE risk than being inactive [22]. In contrast, our findings suggested that the beneficial effect of physical activity was largely restricted to those aged ≥ 65 years. The different 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, whereas the harmful effect in the CHS was restricted to strenuous activity.

We found that active individuals aged ≥ 65 years had a 30% lower VTE risk than 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]. Because of 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. Furthermore, in those aged ≥ 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 a history of CVD and cancer did not modify the risk estimates, the potential for 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 by 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 mechanisms other 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, a wide age distribution, a prospective design with repeated measurements for a part of the study population, and thoroughly validated outcomes. As the 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). Furthermore, as physical activity was assessed via self-report, there is a chance of misclassification (e.g. because of challenges with recall or social desirability). However, as exposure data were collected prior to the occurrence of potential disease, such misclassification is probably independent of the outcome, and not a threat to the internal validity of the study. However, objective assessment strategies (e.g. cardiorespiratory fitness) have a higher level of precision, and have been reported to be superior predictors of all-cause and cancer-related mortality [46,47]. Interestingly, an association between cardiorespiratory fitness in early adulthood and the 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 a lower 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 the *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.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Matrix of categorization based on the light and hard physical activity questions in Tromsø 4 and 5
Table S2. Age-stratified incidence rates and hazard ratios with 95% confidence intervals for provoked and unprovoked VTE by categories of weekly physical activity. The Tromsø Study (1994–2016)
Table S3. Age-stratified incidence rates and hazard ratios with 95% confidence intervals for PE and DVT by categories of weekly physical activity. The Tromsø Study (1994–2016).

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SUPPLEMENT TO:

Repeated assessments of physical activity and risk of incident venous thromboembolism

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Table S1 Matrix of categorization based on the light and hard physical activity questions in Tromsø 4 and 5

		Light physical activity (per week)*			
Hard physical activity (per week)†		**No**	**<1h**	**1-2h**	**≥3h**
	No	1	1	2	3
	<1h	1	1	2	3
	1-2h	4	4	4	4
	≥3h	5	5	5	5

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

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

Table S2 Age-stratified incidence rates and hazard ratios with 95% confidence intervals for provoked and unprovoked 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)§
PROVOKED VTE						
Age <65 years						
Inactive	71 402	40	0.56 (0.41-0.76)	1.00	1.00	1.00
Light PA 1-3 h	56 236	21	0.37 (0.24-0.57)	0.70 (0.41-1.18)	0.74 (0.44-1.27)	0.75 (0.44-1.27)
Light PA >3 h	41 448	18	0.43 (0.27-0.69)	0.77 (0.44-1.35)	0.86 (0.49-1.51)	0.85 (0.49-1.50)
Hard PA 1-3 h	71 506	33	0.46 (0.33-0.65	0.95 (0.59-1.49)	1.02 (0.64-1.63)	1.02 (0.64-1.63)
Hard PA >3 h	30 428	14	0.46 (0.27-0.78)	0.98 (0.54-1.82)	1.12 (0.61-2.07)	1.13 (0.61-2.09)
p for trend				0.94	0.61	0.60
Age ≥65 years						
Inactive	21 363	78	3.65 (2.92-4.56)	1.00	1.00	1.00
Light PA 1-3 h	16 742	46	2.74 (2.06-3.67)	0.77 (0.53-1.10)	0.81 (0.56-1.17)	0.81 (0.56-1.18)
Light PA >3 h	17 644	43	2.44 (1.81-3.29)	0.67 (0.46-0.97)	0.74 (0.50-1.08)	0.74 (0.51-1.09)
Hard PA 1-3 h	10 029	17	1.70 (1.05-2.73)	0.47 (0.28-0.81)	0.51 (0.30-0.87)	0.52 (0.30-0.88)
Hard PA >3 h	4654	11	2.36 (1.31-4.27)	0.66 (0.35-1.24)	0.72 (0.38-1.37)	0.74 (0.39-1.41)
p for trend				0.004	0.018	0.023
UNPROVOKED VTE						
Age <65 years						
Inactive	71 402	31	0.43 (0.31-0.62)	1.00	1.00	1.00
Light PA 1-3 h	56 236	23	0.41 (0.27-0.62)	1.03 (0.60-1.76)	1.13 (0.66-1.95)	1.12 (0.65-1.93)
Light PA >3 h	41 448	17	0.41 (0.25-0.66)	0.97 (0.53-1.76)	1.13 (0.62-2.05)	1.10 (0.60-2.01)
Hard PA 1-3 h	71 506	24	3.34 (0.22-0.50)	0.87 (0.51-1.49)	0.98 (0.57-1.67)	0.99 (0.58-1.69)
Hard PA >3 h	30 428	5	0.16 (0.07-0.39)	0.44 (0.17-1.14)	0.53 (0.20-1.37)	0.53 (0.20-1.37)
p for trend				0.155	0.376	0.386
Age ≥65 years						
Inactive	21 363	41	1.92 (1.41-2.61)	1.00	1.00	1.00
Light PA 1-3 h	16 742	21	1.25 (0.82-1.92)	0.67 (0.40-1.14)	0.71 (0.42-1.21)	0.72 (0.42-1.22)
Light PA >3 h	17 644	29	1.64 (1.14-2.37)	0.87 (0.54-1.41)	0.94 (0.57-1.53)	0.94 (0.57-1.53)
Hard PA 1-3 h	10 029	14	1.40 (0.83-2.36)	0.80 (0.43-1.48)	0.86 (0.46-1.60)	0.86 (0.46-1.62)
Hard PA >3 h	4654	5	1.07 (0.45-2.58)	0.61 (0.24-1.55)	0.67 (0.6-1.71)	0.66 (0.26-1.70)
p for trend				0.518	0.518	0.524

CI confidence interval, *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 S3 Age-stratified incidence rates and hazard ratios with 95% confidence intervals for PE and DVT 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)§
PULMONARY EMBOLISM						
Age <65 years						
Inactive	71 402	32	0.45 (0.32-0.63)	1.00	1.00	1.00
Light PA 1-3 h	56 236	12	0.21 (0.12-0.38)	0.53 (0.27-1.04)	0.59 (0.30-1.15)	0.59 (0.30-1.15)
Light PA >3 h	41 448	9	0.22 (0.11-0.42)	0.50 (0.24-1.06)	0.59 (0.28-1.25)	0.58 (0.28-1.23)
Hard PA 1-3 h	71 506	22	0.31 (0.20-0.47)	0.80 (0.46-1.38)	0.90 (0.52-1.56)	0.91 (0.52-1.57)
Hard PA >3 h	30 428	10	0.33 (0.18-0.61)	0.91 (0.45-1.85)	1.10 (0.54-2.25)	1.09 (0.53-2.24)
p for trend				0.645	0.927	0.922
Age ≥65 years						
Inactive	21 363	51	2.39 (1.81-3.14)	1.00	1.00	1.00
Light PA 1-3 h	16 742	26	1.55 (1.06-2.28)	0.66 (0.41-1.07)	0.70 (0.44-1.13)	0.71 (0.44-1.14)
Light PA >3 h	17 644	32	1.81 (1.28-2.56)	0.76 (0.49-1.19)	0.86 (0.55-1.35)	0.86 (0.55-1.36)
Hard PA 1-3 h	10 029	15	1.50 (0.90-2.48)	0.63 (0.35-1.14)	0.69 (0.38-1.25)	0.70 (0.39-1.26)
Hard PA >3 h	4654	7	1.50 (0.72-3.16)	0.63 (0.28-1.40)	0.71 (0.32-1.58)	0.72 (0.32-1.60)
p for trend				0.093	0.238	0.252
DEEP VEIN THROMBOSIS						
Age <65 years						
Inactive	71 402	39	0.55 (0.40-0.75)	1.00	1.00	1.00
Light PA 1-3 h	56 236	32	0.57 (0.40-0.80)	1.08 (0.67-1.72)	1.15 (0.72-1.84)	1.16 (0.72-1.85)
Light PA >3 h	41 448	26	0.63 (0.43-0.92)	1.14 (0.69-1.88)	1.27 (0.77-2.10)	1.25 (0.76-2.08)
Hard PA 1-3 h	71 506	35	0.49 (0.35-0.68)	1.00 (0.63-1.58)	1.09 (0.69-1.72)	1.09 (0.69-1.73)
Hard PA >3 h	30 428	9	0.30 (0.15-0.57)	0.63 (0.30-1.30)	0.71 (0.34-1.48)	0.72 (0.35-1.50)
p for trend				0.439	0.743	0.760
Age ≥65 years						
Inactive	21 363	68	3.18 (2.51-4.04)	1.00	1.00	1.00
Light PA 1-3 h	16 742	41	2.45 (1.80-3.33)	0.78 (0.53-1.16)	0.83 (0.56-1.23)	0.84 (0.56-1.24)
Light PA >3 h	17 644	40	2.27 (1.66-3.09)	0.72 (0.49-1.07)	0.76 (0.51-1.14)	0.77 (0.51-1.15)
Hard PA 1-3 h	10 029	16	1.60 (0.98-2.60)	0.54 (0.31-0.94)	0.58 (0.33-1.01)	0.58 (0.33-1.02)
Hard PA >3 h	4654	9	1.93 (1.00-3.72)	0.65 (0.32-1.31)	0.70 0.35-1.42)	0.72 (0.35-1.46)
p for trend				0.018	0.045	0.054

CI confidence interval, *DVT* deep vein thrombosis, *HR* hazard ratio, *IR* incidence rate, *PA* physical activity, *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

PAPER III

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ORIGINAL ARTICLE

Cardiorespiratory fitness and future risk of venous thromboembolism

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Abstract

Background: Cardiorespiratory fitness (CRF) is a strong predictor of future arterial cardiovascular disease and premature mortality. However, there are limited data on the association between CRF and the risk of incident venous thromboembolism (VTE).

Objectives: To investigate whether estimated CRF (eCRF) was associated with the risk of incident VTE in a cohort recruited from the general population.

Methods: Participants (n = 10 393) from the sixth survey of the Tromsø Study (2007–08) were included, and incident VTEs were recorded up to 31 December 2016. CRF was estimated in sex-specific algorithms based on age, waist circumference, resting heart rate, and self-reported physical activity. Hazard ratios (HRs) with 95% confidence intervals (CIs) of VTE according to categories of eCRF were estimated in Cox regression models adjusted for sex with age as timescale. The impact of weight status was evaluated in analyses stratified by weight category.

Results: There were 176 incident VTEs during follow-up. Compared with individuals with eCRF < 85% of age-predicted, those with eCRF of 85% to 100% and >100% of age-predicted had 46% (HR 0.54; 95% CI 0.39-0.77) and 67% (HR 0.33; 95% CI 0.20-0.54) lower VTE risk, respectively. Compared with overweight/obese individuals with eCRF < 85% of age-predicted, overweight/obese individuals with eCRF ≥ 85% had 50% (HR 0.50, 95% CI 0.35-0.74) lower risk, and normal weight individuals with eCRF ≥ 85% had 55% (HR 0.45, 95% CI 0.30-0.68) lower risk.

Conclusions: Higher eCRF was associated with lower risk of incident VTE. The association was independent of weight categories, suggesting that higher eCRF may modify the association between obesity and VTE.

KEYWORDS

cardiorespiratory fitness, epidemiology, physical activity, risk factors, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) occurs in 1-2 per 1000 individuals annually and is the third most common lethal cardiovascular disease (CVD) after myocardial infarction and stroke.[1-3] VTE is not only a potentially fatal disease, but is also associated with debilitating complications and high recurrence rates, and is regarded as a significant contributor to the global burden of disease.[4-6] Moreover, with an aging population and a rising prevalence of obesity and cancer, the incidence of VTE is expected to increase in the coming years.[7-9]

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Identification of modifiable risk factors at the population level is currently a priority to curb the growing burden of VTE.

A wealth of evidence supports that regular physical activity is beneficial in the prevention of arterial CVD, some cancers, and type 2 diabetes, as well as for increased longevity.[10,11] Emerging data also support that physical activity is associated with a lower risk of incident VTE,[12-15] although there is some controversy in the literature.[1,16,17] In a recent narrative review, we summarized the available data and concluded that the current literature is balanced toward a small beneficial effect of physical activity.[18] Important challenges in research on physical activity include inconsistent definitions, a variety of available instruments, and the reliance on self-reported data.[18,19] Combined with differences in study design and populations, these challenges may account for the inconsistent literature on physical activity and VTE risk, and studies utilizing objective assessment strategies are warranted.[18]

Cardiorespiratory fitness (CRF) relates to the ability of the circulatory, respiratory, and muscular systems to supply and consume oxygen during sustained physical activity and is quantified as maximal oxygen uptake (VO_{2max}) in liters per minute (L/min) or milliliters per kilogram per minute (mL/kg/min).[20,21] Similar to insufficient physical activity, low CRF is associated with higher risk and less favorable outcomes in arterial CVD and cancer.[22-25] CRF largely reflects the level of habitual physical activity of an individual, but is also influenced by age, sex, genetic architecture, comorbidities, as well as body size and composition.[21,26] Although the gold standard for assessment of CRF is through direct measurement of oxygen uptake by ventilatory expired gas analysis during a maximal exercise test,[27] such testing is time and resource demanding and may not be feasible in clinical and research settings.[22] Therefore, algorithms have been developed to estimate CRF, and these correlate well with objectively assessed CRF and appear to be robust health indicators.[22,28-30] Importantly, CRF is reported to be a stronger predictor than physical activity for several health outcomes, such as coronary heart disease and all-cause mortality.[31-33]

Two previous studies have addressed the association between CRF and risk of incident VTE. On the basis of data from a Swedish cohort of male conscripts (aged 18-20 years), Zöller et al[34] reported that higher weight-adjusted maximal workload on a cycle ergonometric test ($watt_{max}$/kg) was associated with lower risk of unprovoked incident VTE. Further, Kunutsor et al[35] found a non-significant lower VTE risk in middle-aged (42-61 years) men in the highest tertile of weight-adjusted maximal oxygen uptake assessed on a cycle ergonometric test. A limitation of the former study was that 80% of the VTEs occurred before the age of 50 (maximal attained age at the end of follow-up was 56 years), whereas both studies were restricted to men only.[34,35] Thus, it still remains to be established whether CRF relates to VTE risk, and whether an association is influenced by gender. Therefore, the aims of the present study were (a) to investigate the association between estimated CRF (eCRF) and the risk of incident VTE in a cohort recruited from the general population and (b) to explore whether a potential association was influenced by weight as body weight is associated with both CRF and VTE risk.[26,36]

Essentials

- The relation between cardiorespiratory fitness (CRF) and venous thromboembolism (VTE) is unsure.
- We estimated CRF (eCRF) and investigated the association between eCRF and the risk of incident VTE.
- Compared to <85%, an eCRF of 85% to 100% and >100% of predicted was related to 46% and 67% lower risk.
- The association between eCRF and VTE risk was independent of body weight status.

2 | METHODS

2.1 | Study population

The Tromsø Study, initiated in 1974, is a large population-based cohort study with repeated health surveys of the inhabitants of Tromsø, Norway. Seven surveys have been completed so far (2019), and the present study was based on 12 981 participants enrolled in the sixth survey in 2007-2008. Detailed methodology of the Tromsø Study has been published elsewhere.[37] Briefly, total birth cohorts or samples of total birth cohorts of subjects within the age range 30 to 87 years were invited, and the attendance rate was 66%. Individuals not officially registered as inhabitants of the Tromsø municipality at baseline (n = 6), with a history of VTE (n = 182) or with missing data on variables required for estimating CRF (i.e., age, waist circumference, physical activity, and resting heart rate; n = 2400) were excluded. Consequently, 10 393 individuals were included in the analyses. A comparison of included and excluded participants is shown in Table S1. Excluded participants were older, had a larger waist circumference, and had a less favorable cardiovascular risk profile compared with those included. Additionally, the fraction with higher education was lower, and the prevalence of CVD was higher among the excluded. Excluded participants with data on physical activity were more active compared with the included participants. Notably, such data were only available in 421 individuals, and these appeared to be a young selection of the excluded participants (mean age was 53.9 ± 13 years). The study was approved by the Regional Committee for Medical and Health Research Ethics, and all participants provided written informed consent prior to inclusion.

2.2 | Measurements

Baseline information was collected from physical examinations, blood samples, and self-administered questionnaires. Height, weight, blood pressure, and resting heart rate were measured with standardized procedures, as previously described.[36,38] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2), and participants were classified as normal weight (BMI < 25), overweight (BMI 25-29.9), or obese (BMI ≥ 30).[39] Information on leisure-time physical activity, smoking

habits, education, and history of CVD (ie, angina pectoris, myocardial infarction, and stroke) was obtained from self-administered questionnaires.[13,37] The questions on physical activity were related to weekly frequency (never, less than once, once, two to three times or approximately every day), duration per session (<15 min, 15-29 min, 30-60 min, or >1 h), and intensity (not short-winded or sweaty, becoming short-winded or sweaty, or becoming exhausted). A summary physical activity index was calculated by multiplying weighted values of the responses to these questions (Table S2).[40] Data on cancer were obtained from the Cancer Registry of Norway.

2.3 | Estimated cardiorespiratory fitness

Cardiorespiratory fitness (CRF) was estimated from sex-specific algorithms based on age, waist circumference, resting heart rate, and physical activity index.[40] These algorithms were developed and validated in a Norwegian population-based cohort with a wide age range (20-90 years), and CRF estimated from this model has been shown to predict cardiovascular and all-cause mortality.[28,41] The algorithms for estimating CRF (in mL/kg/min) were:[40]

Women (R^2 0.56, standard error of estimate (SEE) 5.14):

$$74.74 - (0.247 \times \text{age}) - (0.259 \times \text{waist circumference}) - (0.114 \times \text{resting heart rate}) + (0.198 \times \text{physical activity index})$$

Men (R^2 0.61,SEE 5.70):

$$100.27 - (0.296 \times \text{age}) - (0.369 \times \text{waist circumference}) - (0.155 \times \text{resting heart rate}) + (0.226 \times \text{physical activity index})$$

In addition, the expected CRF (CRF_{pred}) according to age was calculated for each participant with the formula 55.6 − (0.328 × age) for women, and 63.6 − (0.393 × age) for men.[28] On the basis of the fraction of age-predicted CRF ($eCRF/CRF_{pred}$ * 100%), the participants were divided into three categories with cutoffs at 85% and 100%.[28] Estimated CRF was also expressed as a multiple of the resting metabolic equivalent (MET). One MET is approximately 3.5 mL/kg/min and regarded as a clinically significant change in CRF.[22] Further, the participants were categorized according to age- and sex-specific (by 10 years) quintiles into low eCRF (<20th percentile), moderate eCRF (20-60th percentile), and high eCRF (>60th percentile).[23,28]

2.4 | Identification and adjudication of venous thromboembolism

Incident VTE events during follow-up were identified by searching the hospital discharge registry, the radiology procedure registry, and the autopsy registry at the University Hospital of North Norway (UNN). UNN is the exclusive provider of hospital care and diagnostic radiology in the study region, and the discharge registry comprises both outpatient visits and hospitalizations. Trained personnel reviewed the medical records and adjudicated potential VTE cases. The adjudication criteria were a combination of signs and symptoms of PE or DVT, presence of a thrombus confirmed by radiology, a diagnosis of PE or DVT in the patient's medical record, and initiation of treatment (unless contraindications were specified). Deep vein thromboses in the upper and lower extremities and in other locations (e.g., visceral veins) were included. The process of identification and adjudication of VTE events in the Tromsø Study has previously been described in detail.[42]

All VTEs were classified according to clinical presentation (i.e., DVT or PE with or without DVT) and according to the presence of provoking factors at the time of diagnosis. An event was classified as provoked in the presence of the following factors: 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). The remaining were classified as unprovoked events.

2.5 | Statistical analysis

For each participant, person-years of follow-up were accrued from the date of enrollment in Tromsø 6 (2007-08) to the date of incident VTE, migration, death, or the end of the study period (31 December 2016), whichever occurred first. During follow-up, 630 participants were censored because of migration and 410 because of death.

Crude incidence rates (IRs) with 95% confidence intervals (CIs) were calculated and expressed as number of events per 1000 person-years. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs for total VTE, for provoked and unprovoked VTE, and for PE and DVT. HRs were estimated according to categories of the fraction of age-predicted eCRF, by age- and sex-specific categories of eCRF, and per MET increase. The lowest category was used as the reference in the categorical analyses. Age was used as the timescale, with the age at enrollment defined as entry time and the age at VTE or censoring defined as exit time. The analyses were performed in two models. The basic model was adjusted for age (as timescale) and sex, and the multivariable model was further adjusted for smoking, education, history of CVD, and history of cancer. The analyses of age- and sex-specific categories eCRF were not additionally adjusted for sex. Individuals (n = 79) with missing information on one or more covariates in the multivariable model were omitted from this analysis only. The impact of weight status on the association between eCRF and VTE risk was explored in analyses stratified according to BMI categories (i.e., BMI < 25 and BMI ≥ 25). Statistical interaction between eCRF and sex was tested by including the cross-product term in the proportional hazards regression model and no interaction was found. The proportional hazards assumption was evaluated and verified on the basis of Schoenfeld residuals. The statistical analyses were performed with STATA version 15.1 (Stata Corp).

3 | RESULTS

The mean age at baseline was 56 ± 12 years, and 53.1% of the participants were women. Overall, mean eCRF was 31.5 ± 5.7 mL/kg/min in women and 38.8 ± 6.8 mL/kg/min in men. Baseline characteristics according to categories of fraction of age-predicted eCRF are shown in Table 1, and baseline characteristics according to age- and sex-specific categories of eCRF are shown in Table S3. Absolute eCRF increased with increasing categories from 29.0 mL/kg/min in those with eCRF < 85% of age-predicted to 43.2 mL/kg/min in those with eCRF > 100% of age-predicted. Women were overrepresented in the lowest category (71.2%) and underrepresented in the highest category (19.6%). While the mean age was similar across categories, the cardiovascular risk profile was more favorable in the higher categories of fraction of age-predicted eCRF. The fraction with higher education increased across the categories, while the fraction of current smokers was lowest in the highest category.

During 83 729 person-years of follow-up (median duration: 8.5 years, interquartile range: 8.2-8.9), there were 176 incident VTE events, yielding a crude IR of 2.1 (95% CI 1.8-2.4) per 1000 person-years. Table 2 shows the characteristics of the VTE events. The mean age at incident VTE was 69 ± 11 years, and 55.1% of the events occurred in men. The most common clinical presentation was PE with or without concomitant DVT, accounting for 56.3% of the events, and the remaining 43.7% were isolated DVTs. Further, 60.8% of the events were classified as provoked, with cancer as the most frequent provoking factor (30.7%).

Table 3 shows the association between the fraction of age-predicted eCRF and VTE risk. Compared with those with eCRF < 85% of age-predicted, individuals with eCRF between 85% and 100% and >100% of age-predicted values had 46% (HR 0.54; 95% CI 0.39-0.77) and 67% (HR 0.33; 95% CI 0.20-0.54) lower VTE risk, respectively, in the age- and sex-adjusted model. Significant associations of comparable strength were observed for all outcomes, although those with eCRF > 100% of age-predicted appeared to have a substantially lower risk of unprovoked VTE (HR 0.22; 95% CI 0.09-0.54). The risk estimates were essentially unchanged after further adjustment for smoking, education, history of CVD, and history of cancer. Because of the unequal sex distribution between the categories, the association between fraction of age-predicted eCRF and the risk of total VTE was explored in sex-stratified Cox models. These showed a similar trend to the main analyses, although a stronger association was suggested in women (Table S4). Each MET (approximately 3.5 mL/kg/min) increase in eCRF was associated with a significantly lower risk for all outcomes in the range 21% to 27%.

The impact of weight status on the association between eCRF and VTE was explored in analyses stratified by BMI categories (Figure 1). Compared with the reference group (i.e., overweight/obese individuals with eCRF < 85% of age-predicted), the risk of VTE was 50% (HR 0.50; 95% CI 0.35-0.74) lower among those in the same weight category but with eCRF ≥ 85% of age-predicted. For normal weight individuals with ≥85% of age-predicted eCRF, the risk was 55% lower (HR 0.45; 95% CI 0.30-0.68), whereas normal weight individuals with <85% of age-predicted eCRF had comparable VTE risk to the reference group (HR 1.06; 0.57-1.97).

TABLE 1 Baseline characteristics of participants (*n* = 10 393) by categories of fraction of age-predicted estimated cardiorespiratory fitness (eCRF) [the Tromsø Study (2007-2016)]

	eCRF < 85% (*n* = 3919)	eCRF 85%-100% (*n* = 4508)	eCRF > 100% (*n* = 1966)
eCRF (mL/kg/min)	29.0 ± 4.8	36.5 ± 4.7	43.2 ± 5.7
Age, years (mean, SD)	57 ± 12	55 ± 12	57 ± 12
Sex, women (%, *n*)	71.2 (2790)	52.0 (2342)	19.6 (385)
BMI, kg/m^2 (mean, SD)	29.5 ± 4.4	25.6 ± 3.1	24.1 ± 2.6
Triglycerides, mmol/L (mean, SD)	1.74 ± 1.16	1.43 ± 0.87	1.25 ± 0.74
Total cholesterol, mmol/L (mean, SD)	5.73 ± 1.11	5.54 ± 1.08	5.44 ± 1.02
HDL cholesterol, mmol/L (mean, SD)	1.44 ± 0.41	1.54 ± 0.45	1.60 ± 0.44
Systolic blood pressure, mm Hg (mean, SD)	138 ± 23	132 ± 22	133 ± 22
Smoking (%, *n*)	20.9 (817)	19.0 (855)	13.4 (264)
Higher education[a] (%, *n*)	33.9 (1314)	44.0 (1975)	50.6 (988)
History of CVD (%, *n*)	8.8 (346)	8.3 (372)	10.3 (202)
History of cancer (%, *n*)	6.3 (247)	5.6 (252)	6.1 (120)

Notes: Values are means ± 1 SD or percentages with counts in parentheses.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease (angina pectoris, stroke, myocardial infarction); eCRF, estimated cardiorespiratory fitness; HDL, high-density lipoprotein; SD, standard deviation.
[a]Fifteen or more years of education (corresponding to 3 years in university or academy).

TABLE 2 Characteristics of venous thromboembolism (VTE) events (*n* = 176) [the Tromsø Study (2007-2016)]

	% (*n*)
Age, years (mean, SD)	69 ± 11
Sex (men)	55.1 (97)
Clinical characteristics	
Pulmonary embolism	56.3 (99)
Deep vein thrombosis	43.7 (77)
Provoked	60.8 (107)
Unprovoked[a]	39.2 (69)
Provoking factors[b]	
Surgery	17.1 (30)
Trauma	11.4 (20)
Acute medical condition	9.1 (16)
Cancer	30.7 (54)
Immobilization[c]	14.2 (25)
Other[d]	6.8 (12)
Clinical risk factors	
Estrogens (HRT, oral contraceptives)	3.8 (3)
Heredity[e]	4.0 (7)
Pregnancy/postpartum	1.1 (2)
Other medical conditions[f]	21.3 (23)

Notes: Values are means ± 1 SD or percentages with counts in parentheses.

Abbreviations: HRT, hormone replacement therapy; SD, standard deviation; VTE, venous thromboembolism.

[a]No provoking factors at the time of diagnosis.

[b]One patient may have multiple provoking factors.

[c]Bed rest ≥ 3days, long-distance travel ≥4 h within the previous 14 days, or confined to wheelchair.

[d]Other factors specified as provoking in the medical record (e.g., intravascular catheters).

[e]Reported family history of VTE in first-degree relative(s) before the age of 60.

[f]Other diseases within the previous year (myocardial infarction, ischemic stroke heart failure, inflammatory bowel disease, or myeloproliferative disorders).

HRs for the association between age- and sex-specific categories of eCRF and the risk of incident VTE are shown in Table S5. Compared with individuals with low eCRF, those with moderate and high levels had 37% (HR 0.63; 95% CI 0.44-0.90) and 54% (HR 0.46: 95% CI 0.32-0.68) lower risks, respectively, in the age-adjusted model. The strongest associations were observed in relation to unprovoked VTE and PE. The corresponding risk reductions for those with moderate and high eCRF were 42% (HR 0.58; 95% CI 0.34-1.01) and 64% (HR 0.36; 95% CI 0.19-0.67) for unprovoked VTE and 39% (HR 0.61; 95 CI 0.39-0.96) and 63% (HR 0.37; 95 CI 0.22-0.62) for PE. The risk estimates were essentially unchanged after further adjustment for smoking, education, history of CVD, and history of cancer.

4 | DISCUSSION

In the present study of 10 393 participants recruited from the general population, we found that higher eCRF was associated with a lower risk of incident VTE. This finding was consistent across subcategories of VTE, and a beneficial association between high eCRF and VTE was observed in both normal weight and overweight/obese individuals.

To the best of our knowledge, the association between CRF and the risk of VTE has only been addressed in two previous studies. In a cohort of 777 925 men aged 18 to 20 years, Zöller et al[34] found that one standard deviation increase in maximal workload on a cycle ergonometric test (W_{max}/kg) was associated with 19% lower risk of unprovoked VTE. A direct comparison with our findings is challenging because of different methodology; however, both studies support that a higher fitness level is associated with lower risk of incident VTE.[34] Our findings are also partly supported by Kunutsor et al,[35] who reported that men in the highest tertile of weight-adjusted CRF had a non-significant 20% lower risk of VTE. It was speculated that regression dilution due to a long follow-up (median: 25.2 years), limited statistical power, and study population characteristics may have camouflaged an association.[35] In the present study, we extend previous findings by showing that eCRF was associated with lower VTE risk in individuals of both genders, through a wide age range, across subcategories of VTE (i.e., unprovoked/provoked and DVT/PE) and in both normal weight and overweight/obese subjects.

We found that an eCRF ≥ 85% of age-predicted was associated with 46% lower risk, whereas eCRF > 100% of age-predicted was associated with 67% lower risk, compared with eCRF < 85% of age-predicted. Likewise, moderate (20-60th percentile) and high (>60th percentile) eCRF according to age- and sex-specific categories were associated with 37% and 54% lower VTE risk, respectively, compared with low eCRF (<20th percentile). These risk estimates are somewhat larger than those observed in studies on physical activity and VTE, where risk reductions between 4% and 41% have been reported.[12-15] A stronger association between eCRF and VTE may be ascribed to several factors. First, information on habitual physical activity is commonly obtained through self-report,[12-15] with an inherent chance of misclassification due to challenges with recall and social desirability.[19] In cohorts, such misclassification would be non-differential and presumably lead to underestimation of the true risk.[43] Thus, it is likely that the association between physical activity and VTE is stronger than currently perceived. Estimated CRF also comprises additional components that are measured with a high level of precision, and that are well-established risk factors for VTE, such as waist circumference and age, which were the two most heavily weighted components in the eCRF algorithm. Obesity is associated with a twofold to threefold increased risk of VTE, and among the obesity measures, waist circumference is reported to be the strongest predictor of VTE.[44,45] Further, although VTE may occur at all ages, the incidence increases exponentially with age, and the risk in those ≥85 years is more than 12-fold higher than in those aged 45 to 55 years.[3,17] Finally, as a sizable proportion of the variance in CRF

TABLE 3 Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) according to percentage of age-predicted estimated cardiorespiratory fitness (eCRF) [the Tromsø Study (2007-2016)]

Fraction of age-predicted eCRF	Person-years	VTE events	Crude IR (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]
Total VTE					
<85%	31 339	94	3.00 (2.45-3.67)	1	1
85%-100%	36 438	60	1.65 (1228-2.12)	0.54 (0.39-0.77)	0.54 (0.39-0.76)
>100%	15 951	22	1.38 (0.91-2.09)	0.33 (0.20-0.54)	0.33 (0.20-0.54)
Per 1 MET	83 729	176	2.10 (1.81-2.44)	0.75 (0.67-0.83)	0.75 (0.67-0.83)
Provoked VTE					
<85%	31 339	57	1.82 (1.40-2.36)	1	1
85%-100%	36 438	34	0.93 (0.67-1.31)	0.53 (0.34-0.82)	0.52 (0.33-0.81)
>100%	15 951	16	1.00 (0.61-1.64)	0.41 (0.23-0.75)	0.41 (0.23-0.75)
Per 1 MET	83 729	107	1.28 (1.06-1.54)	0.76 (0.66-0.87)	0.76 (0.66-0.87)
Unprovoked VTE					
<85%	31 339	37	1.18 (0.86-1.63)	1	1
85%-100%	36 438	26	0.71 (0.49-1.05)	0.58 (0.34-0.97)	0.57 (0.34-0.96)
>100%	15 951	6	0.38 (0.17-0.84)	0.22 (0.09-0.54)	0.22 (0.09-0.53)
Per 1 MET	83 729	69	0.82 (0.65-1.04)	0.73 (0.62-0.87)	0.73 (0.61-0.86)
Pulmonary embolism					
<85%	31 339	51	1.63 (1.24-2.14)	1	1
85%-100%	36 438	35	0.96 (0.69-2.14)	0.56 (0.36-0.88)	0.55 (0.35-0.86)
>100%	15 951	13	0.81 (0.47-1.40)	0.32 (0.17-0.61)	0.32 (0.17-0.61)
Per 1 MET	83 729	99	1.18 (0.97-1.40)	0.72 (0.62-0.83)	0.72 (0.62-0.83)
Deep vein thrombosis					
<85%	31 339	43	1.37 (1.02-1.85)	1	1
85%-100%	36 438	25	0.67 (0.46-1.02)	0.53 (0.32-0.88)	0.52 (0.31-0.87)
>100%	15 951	9	0.56 (0.29-1.08)	0.35 (0.16-0.75)	0.35 (0.16-0.75)
Per 1 MET	83 729	77	0.92 (0.74-1.15)	0.79 (0.67-0.93)	0.79 (0.67-0.93)

Notes: Abbreviations: MET, metabolic equivalent (3.5 mL/kg/min).
[a]Adjusted for age (as time scale) and sex.
[b]Adjusted for age (as time scale), sex, smoking, education, history of cardiovascular disease, and history of cancer.

may be ascribed to inherited factors, a highly active individual may have a relatively low level of fitness, and vice versa.[21,46] Therefore, it has been suggested that physical activity and CRF may be considered as independent entities.[31]

Analyses stratified by BMI categories revealed that eCRF may alter the relationship between weight status and VTE risk. Specifically, we found that overweight and obese individuals with ≥85% of age-predicted eCRF had comparable VTE risk to normal weight individuals, and that the risk in normal weight individuals with eCRF < 85% was comparable to the risk in individuals with a high body weight. This suggests that the association between eCRF and VTE is independent of weight categories, and that higher eCRF may mitigate the elevated VTE risk in overweight/obesity. Similar observations have been made in relation to other major health outcomes, including all-cause and CVD mortality, and CRF is also reported to influence the obesity paradox such that no paradox is observed in individuals who are classified as fit.[47,48] The present findings are in line with our previous report on physical activity and VTE risk, where we found that the association was only partly mediated by BMI (14%-36%), and concluded that the effect of physical activity on VTE risk primarily must be ascribed to mechanisms other than obesity.[13]

The study by Zöller et al[34] explored the role of familial components on the association between CRF and VTE risk. Attenuation of the risk estimates in analyses restricted to cousins and full siblings suggested that the association was partly confounded by familial factors.[34] It is well established that the level of CRF in sedentary individuals and the ability to increase CRF with exercise demonstrate a high degree of familial aggregation and heritability. The familial resemblance of CRF is approximately 50%, and the genetic component is estimated to be 20% to 30% in sedentary individuals.[21,46] There are also large interindividual variations in the responses to exercise, with a familial resemblance of approximately 50%.[49] The field of exercise genomics is still in its early stages and characterized by

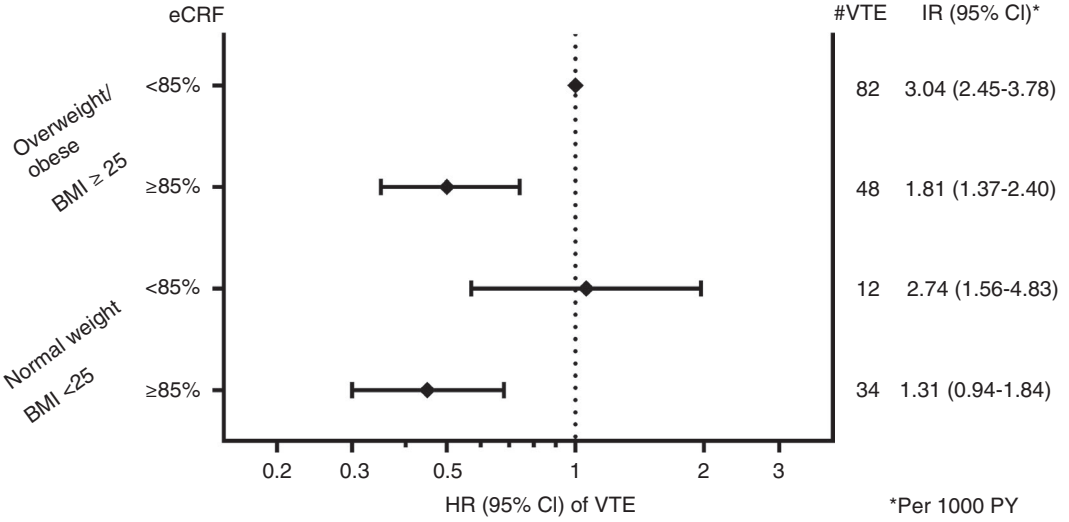

FIGURE 1 Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) by percentage of age-predicted estimated cardiorespiratory fitness (eCRF) and weight status [the Tromsø Study (2007-2016)]. The regression model is adjusted for age (as time scale) and sex. BMI, body mass index; PY, person-years

underpowered and heterogeneous studies awaiting replication.[50,51] Although we currently are not aware of any genetic variants related to CRF that have been identified in genome-wide association studies of VTE, future adequately powered studies may investigate a potential causal association between CRF and VTE using a Mendelian randomization design.[52-54]

At present, there is a lack of consensus on the definition of low, moderate, and high levels of CRF.[22] Previous studies on CRF in relation to other health outcomes have used a variety of measures such as study-specific percentiles, age-specific cutoff values, and absolute cutoffs.[23,28,55,56] In the present study, we found that higher eCRF was associated with lower VTE risk when expressed as a fraction of age-predicted values, age- and sex-specific categories, and per-MET increase. However, the former approach appeared to be superior as it was most strongly associated with VTE risk and was consistently associated with VTE risk across all subcategories. Considering CRF relative to the expected values for a healthy individual may not only be an easily communicable format in clinical and public health settings,[57] but also facilitate comparison between studies.

The main strengths of the present study include participants recruited from a general population with a wide age range, high participation rates, and a thoroughly validated outcome. The UNN is the only provider of relevant diagnostics and hospital care in the study region, and a near-complete register may be anticipated. The present study is among the first to present data on the association between CRF and VTE risk and provides highly relevant knowledge to the field of lifestyle factors and VTE risk. Limitations of the study include a substantial amount of exclusions (18%) due to missing values on variables necessary to estimate CRF. Excluded participants were older and had a less favorable cardiovascular risk profile compared with those included. Although this may hamper the generalizability of our findings, it is unlikely to be a threat to the internal validity of the study. Furthermore, information on physical activity used in the eCRF algorithm was collected via self-report, with an inherent chance of information bias. However, given the prospective design of our study, this would be non-differential and tend to bias the association toward the null.[43] Finally, because of the observational design, there is a chance for residual confounding due to unknown confounders.

In conclusion, we found that higher eCRF, obtained from easily available variables, was associated with a lower risk of incident VTE. The association was independent of weight status, suggesting that eCRF may counterbalance the elevated VTE risk associated with a high body weight.

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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CONFLICTS OF INTERESTS

L. H. Evensen, T. Isaksen, S. K. Brækkan, and J.-B. Hansen report no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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SUPPLEMENT TO:

Cardiorespiratory fitness and future risk of venous thromboembolism

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Table S1 Comparison of baseline characteristics in included and excluded participants

	Included (n=10,393)	**Excluded (n=2,400)**
Age, years (mean, SD)	56 ± 12	63 ± 14
Sex, women (%, n)	53.1 (5,517)	55.3 (1,326)
BMI, kg/m^2 (mean, SD)	26.8 ± 4.1	27.3 ± 4.6
Waist circumference, cm (mean, SD)	94.5 ± 12.1	96.9 ± 12.7*
Triglycerides, mmol/L (mean, SD)	1.51 ± 0.99	1.59 ± 0.91
Total cholesterol, mmol/L (mean, SD)	5.59 ± 1.08	5.67 ± 1.14
HDL cholesterol, mmol/L (mean, SD)	1.52 ± 0.44	1.48 ± 0.43
Systolic blood pressure, mmHg (mean, SD)	135 ± 23	140 ± 24
Smoking (%, n)	18.6 (1,936)	26.4 (633)
Higher education† (%, n)	41.5 (4,277)	21.9 (503)
History of CVD (%, n)	8.9 (920)	16.6 (398)
History of cancer (%, n)	6.0 (619)	8.0 (192)
Physical activity index (mean, SD)	7.7 ± 9.1	9.1 ± 10.0‡

BMI, body mass index; CVD, cardiovascular disease (angina pectoris, stroke, myocardial infarction); HDL, high-density lipoprotein; SD, standard deviation

*Among the excluded participants, 1,938 had data on waist circumference

†Fifteen or more year of education (corresponding to 3 years in university or academy)

‡Among the excluded participants, 421 had data on physical activity

Values are means ± 1 SD or percentages with counts in parentheses

Table S2 Physical activity index [1]

Question	Answer	Points given
How frequently do you exercise?	Never	0
	Less than once a week	0
	Once a week	1
	Two or three times a week	2
	Almost every day	3
How hard do you exercise?	Take it easy	0
	Heavy breath and sweat	5
	Push near exhaustion	10
How long does each session last?	<15 min	1
	16-30 min	1
	30-60 min	1.5
	>1 h	1.5

Table S3 Baseline characteristics of participants (n=10,393) stratified by categories of estimated cardiorespiratory fitness (eCRF); the Tromsø Study (2007-2016)

	Low eCRF* **(n=2,085)**	**Moderate eCRF*** **(n=4,158)**	**High eCRF*** **(n=4,150)**
eCRF (mL/kg/min)	28.2 ± 5.3	33.8 ± 5.5	39.4 ± 6.5
Age, years (mean, SD)	57 ± 13	56 ± 12	56 ± 12
Sex, women (%, n)	53.1 (1,106)	53.1 (2,208)	53.1 (2,203)
BMI, kg/m^2 (mean, SD)	31.4 ± 4.3)	27.0 ± 3.2	24.3 ± 2.8
Triglycerides, mmol/L (mean, SD)	1.93 ± 1.37	1.58 ± 0.90)	1.25 ± 0.74
Total cholesterol, mmol/L (mean, SD)	5.65 ± 1.10	5.67 ± 1.09	5.49 ± 1.06
HDL cholesterol, mmol/L (mean, SD)	1.34 ± 0.38	1.47 ± 0.40	1.65 ± 0.45
Systolic blood pressure, mmHg (mean, SD)	140 ± 22	135 ± 22	131 ± 23
Smoking (%, n)	21.8 (454)	20.1 (835)	15.6 (647)
Higher education† (%, n)	32.3 (666)	40.0 (1,651)	47.5 (1,960)
History of CVD (%, n)	10.5 (219)	8.7 (363)	8.1 (338)
History of cancer (%, n)	6.5 (135)	6.2 (258)	5.5 (226)

BMI, body mass index; CVD, cardiovascular disease (angina pectoris, stroke, myocardial infarction); SD, standard deviation; HDL, high-density lipoprotein.

*Low, moderate, and high eCRF were defined as the lowest 20%, the next 40%, and the highest 40%, respectively, according to the age (by ten years) and sex-specific distribution.

†Fifteen or more year of education (corresponding to 3 years in university or academy).

Values are means ± 1 SD or percentages with counts in parentheses.

Table S4 Sex-specific incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) according to percentage of age-predicted cardiorespiratory fitness (CRF); the Tromsø Study (2007-2016)

Fraction of age-predicted CRF	Person-years	VTE events	Crude IR (95% CI)	HR (95% CI)*	HR (95% CI)†
Women					
<85%	22461	59	2.63 (2.04-3.39)	1	1
85-100%	19110	18	0.94 (0.59-1.50)	0.43 (0.25-0.73)	0.43 (0.25-0.74)
>100%	3166	2	0.63 (0.16-2.53)	0.26 (0.06-1.07)	0.27 (0.07-1.11)
Per 1 MET	44737	79	1.77 (1.42-2.20)	0.67 (0.56-0.80)	0.67 (0.56-0.81)
Men					
<85%	8878	35	3.94 (2.83-5.49)	1	1
85-100%	17329	42	2.42 (1.79-3.28)	0.65 (0.42-1.02)	0.64 (0.41-1.00)
>100%	12785	20	1.56 (1.01-2.42)	0.37 (0.21-0.64)	0.36 (0.21-0.62)
Per 1 MET	38991	97	2.49 (2.04-3.04)	0.79 (0.70-0.91)	0.79 (0.69-0.90)

MET, metabolic equivalent (3.5 mL/kg/min)

*Adjusted for age (as timescale)

†Adjusted for age (as timescale), smoking, education, history of cardiovascular disease and history of cancer.

Table S5 Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) by categories of estimated cardiorespiratory fitness (eCRF); the Tromsø Study (2007-2016)

eCRF*	Person-years	VTE events	Crude IR (95% CI)	HR (95% CI)†	HR (95% CI)‡
Total VTE					
Low eCRF	16501	56	3.93 (2.61-4.41)	1	1
Moderate eCRF	33534	70	2.09 (1.65-2.64)	0.63 (0.44-0.90)	0.63 (0.44-0.89)
High eCRF	33694	50	1.48 (1.12-1.96)	0.46 (0.32-0.68)	0.46 (0.32-0.68)
Provoked VTE					
Low eCRF	16501	32	1.94 (1.37-2.74)	1	1
Moderate eCRF	33534	42	1.25 (0.93-1.69)	0.66 (0.42-1.05)	0.66 (0.42-1.05)
High eCRF	33694	33	0.98 (0.70-1.38)	0.54 (0.33-0.88)	0.55 (0.33-0.89)
Unprovoked VTE					
Low eCRF	16501	24	1.45 (0.97-2.17)	1	1
Moderate eCRF	33534	28	0.83 (0.58-1.21)	0.58 (0.34-1.01)	0.58 (0.34-1.01)
High eCRF	33694	17	0.50 (0.31-0.81)	0.36 (0.19-0.67)	0.35 (0.19-0.66)
Pulmonary embolism					
Low eCRF	16501	34	2.06 (1.47-2.88)	1	1
Moderate eCRF	33534	41	1.22 (0.90-1.66)	0.61 (0.39-0.96)	0.61 (0.38-0.95)
High eCRF	33694	24	0.71 (0.48-1.06)	0.37 (0.22-0.62)	0.37 (0.22-0.62)
Deep vein thrombosis					
Low eCRF	16501	22	1.33 (0.88-2.02)	1	1
Moderate eCRF	33534	29	0.86 (0.60-1.24)	0.66 (0.38-1.16)	0.66 (0.38-1.16)
High eCRF	33694	26	0.77 (0.53-1.13)	0.61 (0.35-1.08)	0.61 (0.35-1.08)

*Low, moderate, and high eCRF were defined as the lowest 20%, the next 40%, and the highest 40%, respectively, according to the age (by ten years) and sex-specific distribution.

†Adjusted for age (as timescale)

‡Adjusted for age (as timescale), smoking, education, history of cardiovascular disease and history of cancer.

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1 Nes BM, Janszky I, Vatten LJ, Nilsen TI, Aspenes ST, Wisloff U. Estimating V.O 2peak from a nonexercise prediction model: the HUNT Study, Norway. *Med Sci Sports Exerc* 2011; 43: 2024-30.

PAPER IV

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ORIGINAL ARTICLE

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

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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 patients with VTE recruited from the general population.

Methods: Patients with incident VTE (n = 786) derived from the Tromsø Study surveys 4-6 (1994-1995, 2001-2002, and 2007-2008) were included, and data on physical activity were dichotomized according to the activity level reported in the survey preceding the incident VTE (inactive: <1 hour per week, active: ≥1 hour 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 10 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 (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 deep vein thrombosis.

KEYWORDS
epidemiology, physical activity, recurrence, risk factors, venous thromboembolism

1 | 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, postthrombotic syndrome, 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 10-year cumulative recurrence extends to 30%-40%.[4,7,8] Characteristics of the incident event,

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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 with the general population, especially during the first year after the event.[12,13] The 1-, 5-, and 10-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 resulting from 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 compared with <1 hour per week, with limited evidence of additional benefits with increasing amounts of activity.[19] The role of physical activity regarding 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) before the incident VTE had a 1.5-fold higher risk of recurrence, whereas no association was observed in men.[22] 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 aware of only one study investigating this association in patients with VTE.[25] Faller et al[25] found that elderly VTE patients (≥65 years) with a low activity level had an almost two-fold increased risk of mortality during 3 years of follow up. 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 before the incident event and the risk of (a) recurrent VTE and (b) all-cause mortality in a cohort of VTE patients recruited from a general population.

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 associated with recurrence risk, but with 28% lower risk of mortality.
- This association was most pronounced in patients with incident deep vein thrombosis.

2 | METHODS

2.1 | Study population

The source population comprised 30 586 individuals participating in one or more of the Tromsø Study surveys 4 (1994-1995), 5 (2001-2002), and 6 (2007-2008). 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 prebaseline 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 before 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 (1994-1995, 2001-2002, or 2007-2008) 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, which 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 because of missing information on physical activity in the last survey they participated in before the VTE event, yielding 786 VTE patients eligible for the present study.

2.2 | 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 eight weeks

before 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 hours 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.

2.3 | 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 were 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, 1-2, 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, 15-29, 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 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 in which 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."

2.4 | Outcome registration

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

2.5 | 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), 1 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). The 1-, 5-, and 10-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, whereas model 2 included model 1 + BMI, history of CVD, and cancer-related VTE. Because of a 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; and model 3 included model 2 + history of CVD and cancer-related VTE. Incidence rates and HRs according to physical activity status were estimated for overall recurrence and mortality with 1, 5, and 10 years of follow up, and in subgroups stratified by characteristics of the incident events with 10 years of follow up. Because of high mortality in patients with cancer-related VTE, the stratified analyses were restricted to 5 years of follow up for recurrence and mortality in this group. There were five 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] To take competing risk by death into account, cumulative incidence functions and subdistribution hazard ratios (SHRs) 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. Because 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 before 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.

3 | 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 (noncancer) 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 noncancer-provoked events was similar between active and inactive, whereas 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, whereas 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 (±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.

3.1 | 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

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 (y), mean (±SD)	70 (±14)	66 (±13)
Sex (women), % (n)	58.2 (146)	47.7 (255)
Body mass index (kg/m^2), mean (±SD)[a]	27.8 (±5.1)	27.1 (±4.4)
Education, % (n)[a]	18.0 (44)	23.8 (126)
Current smoking, % (n)[a]	29.1 (73)	28.6 (153)
History of cardiovascular disease, % (n)[b]	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[c]	29.9 (75)	26.5 (142)
Provoked[d]	33.5 (84)	34.4 (184)
Planned treatment duration with AC, % (n)		
0-3 mo	36.7 (92)	35.5 (190)
3-6 mo	31.5 (79)	36.5 (195)
6-12 mo	21.5 (54)	18.5 (99)
>12 mo	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[e]	20.7 (52)	16.5 (88)
Other provoking factor[f]	6.0 (15)	4.1 (22)
Clinical risk factors, % (n)		
Obesity[g]	22.2 (54)	16.3 (84)
Family history[h]	2.0 (5)	3.9 (21)
Other medical conditions[i]	30.7 (67)	16.9 (79)
Pregnancy/postpartum (of cases in women)	0.68 (1)	1.96 (5)
Estrogen use (of cases in women)[j]	9.7 (14)	10.6 (27)

Note: Values are mean (SD) or percentage (count).
AC, anticoagulants; SD, standard deviation; VTE, venous thromboembolism.
[a]Assessed at the most recent survey before the incident VTE event.
[b]Angina pectoris, stroke, or myocardial infarction.
[c]Active cancer or cancer diagnosed within 1 y after the VTE event.
[d]Excluding cancer.
[e]Bed rest ≥3 d, long-distance travel ≥4 h within the previous 14 d, or confined to wheelchair.
[f]Other factors specified as provoking in the medical record (e.g., intravascular catheters).
[g]Body mass index ≥30 kg/m^2 at the time of incident VTE.
[h]Reported family history of VTE in first-degree relative(s) before the age of 60.
[i]Other diseases within the previous year (myocardial infarction, ischemic stroke heart failure, inflammatory bowel disease, or myeloproliferative disorders).
[j]Hormone replacement therapy or oral contraceptives.

individuals throughout follow-up (Figure 1). At 1 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 5 years, and 25.2% (95% CI 17.0-36.3) and 31.3 (95% CI 25.9-37.5) at 10 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 with inactive individuals, particularly at 1 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 5 years (HR model 2: 1.27, 95% CI 0.68-2.35) and 10 years (HR model 2: 1.48, 95% CI 0.83-2.65). Similarly, when analyses were conducted across five levels of physical activity for 10-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 5- and 10-year risk estimates were close to one, but in opposite directions. Notably, there were very few recurrences (n = 7) between 5 and 10 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 10-year recurrence risk with high weekly activity (Table S1).

Analyses of the 10-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).

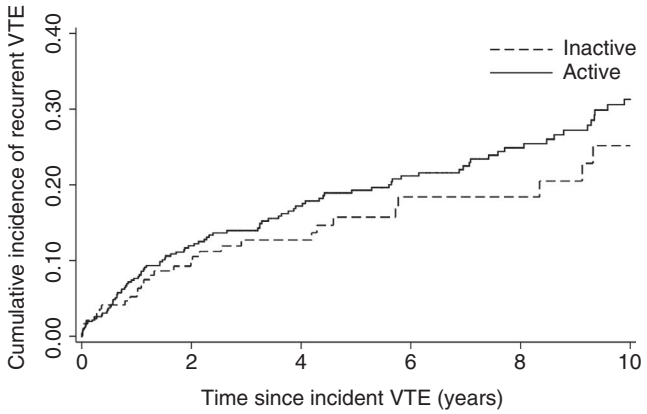

FIGURE 1 Cumulative incidence of venous thromboembolism (VTE) recurrence according to physical activity status (inactive: <1 h per wk, active: ≥1 h per wk). The Tromsø Study 1994-2015

3.2 | 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 Figure 2, the 10-year survival probability was lower in inactive compared with active individuals. The cumulative mortality at 1 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 5 years (48.5%, 95% CI 42.1-55.3 vs 35.7%, 95% CI 31.6-40.0) and 10 years of follow-up (65.2%, 95% CI 57.9-72.4 vs 49.0%, 95% CI 44.4-53.9). The adjusted 1-, 5-, and 10-year mortality risk according to physical activity status are shown in Table 5. There was a non-significant trend of a lower 1-year mortality risk among active individuals (HR model 3: 0.81, 95% CI 0.57-1.17). At 5 and 10 years of follow-up, the fully adjusted mortality risk was significantly 25% and

TABLE 2 Incidence rates and hazard ratios with 95% confidence intervals for 1-, 5-, and 10-y venous thromboembolism recurrence by physical activity status (The Tromsø Study 1994-2015)

	Person-years	Events	Crude IR (95% CI)[a]	HR model 1 (95% CI)[b]	HR model 2 (95% CI)[c]	SHR (95% CI)[c]
1-y 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)
5-y 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)
10-y 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)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, subdistribution hazard ratio.

[a]Per 100 person-years.

[b]Adjusted for age and sex.

[c]Model 1 + body mass index, history of cardiovascular disease and cancer-related venous thromboembolism.

TABLE 3 Incidence rates and hazard ratios with 95% confidence intervals for 5- and 10-y venous thromboembolism recurrence by physical activity status stratified by sex (The Tromsø Study 1994-2015)

	Person-years	Events	Crude IR (95% CI)[a]	HR model 1 (95% CI)[b]	HR model 2 (95% CI)[c]	SHR (95% CI)[c]
5-y 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)
10-y 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)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, subdistribution hazard ratio.
[a]Per 100 person-years.
[b]Adjusted for age.
[c]Model 1 + body mass index, history of cardiovascular disease and cancer-related venous thromboembolism.

TABLE 4 Incidence rates and hazard ratios with 95% confidence intervals for 10-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)[a]	HR model 1 (95% CI)[b]	HR model 2 (95% CI)[c]	SHR (95% CI)[c]
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[d]						
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)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, subdistribution hazard ratio.
[a]Per 100 person-years.
[b]Adjusted for age and sex.
[c]Model 1 + body mass index.
[d]Follow-up restricted to 5 y.

28% lower, respectively, in active compared with inactive individuals. In analyses of the 10-year mortality risk across five categories of physical activity, there was a threshold effect in which light physical activity ≥1 hour per week (>the reference category) was associated with a lower risk compared with <1 hour per week, with no additional benefit with increasing amounts of physical activity (Table S2).

Table 6 shows the 10-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), whereas no association was observed for cancer-related VTE (5-year mortality risk reported because of high mortality rates). The 10-year cumulative mortality rates and risks according to physical activity status for PE and DVT are shown in Figure 3A, B and Table 6. Although no significant association was observed in patients with PE (HR model 2: 0.87, 95% CI 0.61-1.26), the 10-year mortality risk following DVT was 41% lower among active compared with inactive individuals (HR model 2: 0.59, 95% CI 0.44-0.79).

3.3 | Competing risk by death

The cumulative incidence of recurrence dropped when competing risk by death was taken into account. At 1, 5, and 10 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 form the Cox regression (Tables 2–4 and Table S1).

4 | 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 (a) physical activity was associated with a lower risk of mortality, (b) the inverse association appeared mainly in patients with DVT as the incident event, and (c) 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 1-10 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]

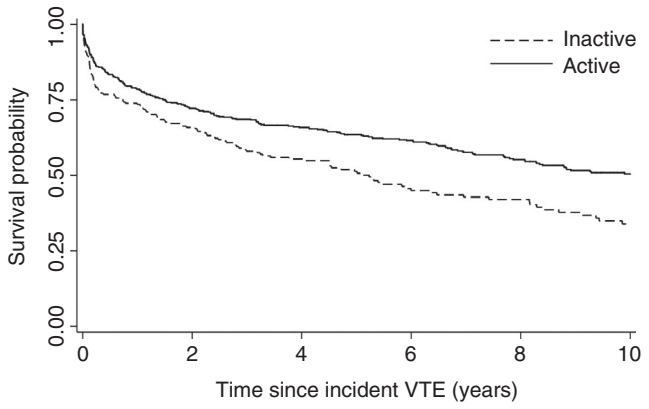

FIGURE 2 Survival probability after venous thromboembolism (VTE) according to physical activity status (inactive: <1 h per wk, active: ≥1 h per wk). The Tromsø Study 1994-2015

The beneficial association between physical activity and mortality mainly appeared in patients with DVT as the incident event, whereas no clear association was observed in relation to PE. Compared with 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 with DVT in the present study.

In contrast to our findings, Faller et al[25] reported that the inverse association between physical activity and mortality was largely driven by an effect in patients with PE (± DVT). There are several plausible explanations for the apparently diverging findings. Faller et al assessed physical activity habits at the time of the incident VTE, whereas we used data obtained before 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 a PE without additional radiological procedures. The prevalence of PE was high (69%) compared with 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 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

TABLE 5 Mortality rates and hazard ratios with 95% confidence intervals for 1-, 5-, and 10-y mortality in patients with incident venous thromboembolism by physical activity status (The Tromsø Study 1994-2015)

	Person-years	Deaths	Crude MR (95% CI)[a]	HR model 1 (95% CI)[b]	HR model 2 (95% CI)[c]	HR model 3 (95% CI)[d]
1-y 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)
5-y 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)
10-y 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)

Abbreviations: CI, confidence interval; HR, hazard ratio; MR, mortality rate.
[a]Per 100 person-years.
[b]Adjusted for age (as time scale) and sex.
[c]Model 1 + body mass index, current smoking and education.
[d]Model 2 + history of cardiovascular disease and cancer-related venous thromboembolism.

TABLE 6 Mortality rates and hazard ratios with 95% confidence intervals for 10-y 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)[a]	HR model 1 (95% CI)[b]	HR model 2 (95% CI)[c]
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[d]					
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)

Abbreviations: CI, confidence interval; HR, hazard ratio; MR, mortality rate.
[a]Per 100 person-years.
[b]Adjusted for age (as time scale) and sex.
[c]Model 1 + body mass index, education and current smoking.
[d]Follow-up restricted to 5 y.

the MEGA follow-up study, Flinterman et al[22] found that a sedentary lifestyle (prolonged sitting) assessed at the time of incident VTE was associated with an increased risk of recurrence in women, whereas no association was observed in men. Because it is possible for an individual to accumulative 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 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 in which a risk factor is differently related to first and recurrent events.[38] Because the risk of incident

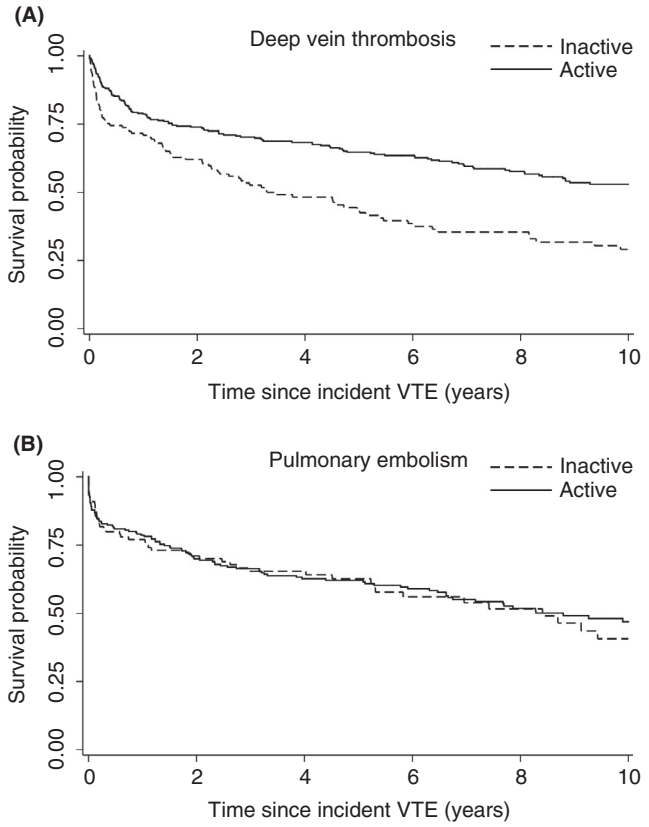

FIGURE 3 Survival probability after venous thromboembolism (VTE) in patients with (A) incident deep vein thrombosis and (B) pulmonary embolism according to physical activity status (inactive: <1 h per wk, active: ≥1 h per wk). The Tromsø Study 1994-2015

and recurrent VTE is 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 from 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 before the incident event. In the subgroup of patients who returned to a survey after their incident event, 75% remained at the same activity level, whereas 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 5 years of aging, which was particularly pronounced in those with PE.[3] There are several consequences of VTE that may influence the postevent activity level, such as postthrombotic syndrome, chronic pulmonary thromboembolic pulmonary hypertension, impaired physical function and capacity, and 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, nondifferential 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. Because the University Hospital of North Norway 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 nonresponders. Further, because physical activity was assessed via self-report, there is a chance for misclassification (e.g., from 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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CONFLICT OF INTERESTS

L.H. Evensen, T. Isaksen, S.K. Brækkan, and J.-B. Hansen report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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SUPPLEMENT TO:

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

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Table S1

Overall and sex-stratified incidence rates and hazard ratios with 95% confidence intervals for ten-year recurrence in patients with incident venous thromboembolism across categories of weekly physical. 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)‡
All						
Inactive	882	31	3.51 (2.47-5.00)	1	1	1
Light PA 1-3 h	779	33	4.23 (3.01-5.96)	1.25 (0.76-2.05)	1.23 (0.75-2.01)	1.44 (0.88-2.36)
Light PA >3 h	752	29	3.86 (2.68-5.55)	1.20 (0.72-1.99)	1.15 (0.69-1.93)	1.25 (0.75-2.08)
Hard PA 1-3 h	533	24	4.50 (3.02-6.71)	1.25 (0.73-2.16)	1.25 (0.73-2.17)	1.47 (0.87-2.48)
Hard PA >3 h	289	12	4.15 (2.35-7.30)	1.17 (0.60-2.31)	1.34 (0.67-2.66)	1.29 (0.68-2.44)
Men						
Inactive	343	14	4.08 (2.42-6.89)	1	1	1
Light PA 1-3 h	402	19	4.73 (3.02-7.41)	1.28 (0.64-2.57)	1.22 (0.61-2.45)	1.56 (0.78-3.12)
Light PA >3 h	261	15	5.75 (3.47-9.55)	1.39 (0.67-2.90)	1.40 (0.67-2.93)	1.47 (0.72-3.04)
Hard PA 1-3 h	354	21	5.92 (3.86-9.09)	1.62 (0.82-3.19)	1.65 (0.83-3.26)	2.00 (1.03-3.91)
Hard PA >3 h	202	12	5.94 (3.37-10.46)	1.75 (0.80-3.84)	1.94 (0.87-4.28)	1.83 (0.86-3.91)
Women						
Inactive	539	17	3.15 (1.96-5.07)	1	1	1
Light PA 1-3 h	378	14	3.71 (2.20-6.26)	1.24 (0.61-2.51)	1.20 (0.59-2.44)	1.27 (0.61-2.63)
Light PA >3 h	491	14	2.85 (1.69-4.81)	1.01 (0.50-2.06)	0.95 (0.46-1.97)	1.07 (0.51-2.23)
Hard PA 1-3 h	179	3	1.68 (0.54-5.20)	0.62 (0.18-2.15)	0.66 (0.19-2.30)	0.68 (0.20-2.33)
Hard PA >3 h	87	0	n/a	n/a	n/a	n/a

*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, *PA* physical activity, *SHR* subdistribution hazard ratio, *VTE* venous thromboembolism.

Table S2

Mortality rates and hazard ratios with 95% confidence intervals for ten-year mortality in patients with incident venous thromboembolism across categories of weekly physical activity. 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)§
Total VTE						
Inactive	983	136	13.83 (11.69-16.37)	1	1	1
Light PA 1-3 h	935	76	8.13 (6.49-10.18)	0.66 (0.49-0.87)	0.64 (0.48-0.86)	0.65 (0.48-0.88)
Light PA >3 h	859	89	10.37 (8.42-12.76)	0.73 (0.56-0.96)	0.69 (0.52-0.91)	0.73 (0.55-0.98)
Hard PA 1-3 h	652	40	6.13 (4.50-8.36)	0.62 (0.43-0.89)	0.64 (0.44-0.92)	0.69 (0.47-1.02)
Hard PA >3 h	333	24	7.21 (4.84-10.76)	0.68 (0.44-1.06)	0.72 (0.46-1.13)	1.23 (0.78-1.96)

*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, *PA* physical activity, *VTE* venous thromboembolism