UiT The Arctic University of Norway

Faculty of Health Sciences

Differences in risk of venous thromboembolism in men and women

Carl Arne Løchen Arnesen

June 2024

A dissertation for the degree of Philosophiae Doctor (PhD)

Content

Acknowledgements

Work on this thesis was carried out at the K.G. Jebsen Thrombosis Research and Expertise Center (TREC), later named Thrombosis Research Center (TREC) at the department of Clinical Medicine, UiT – The Arctic University of Norway between August 2019 and March 2024. For most of this period (2019-2023), I was part of the MD/PhD program for medical students and during the final six months, I worked full-time as a PhD fellow at UiT with funding from The Northern Norway Regional Health Authorities.

First and foremost, I must thank my main supervisor, Professor Sigrid K. Brækkan. I could not have asked for a better guide through the labyrinthine landscape of research. You have been an inspiration throughout the entire process, and your dedication to your work has never ceased to impress me. Annoyingly, you are equally skilled in almost every other area in life, and one of the kindest people I have ever met. I have been incredibly lucky to have had you as my supervisor, and I am eternally grateful for everything you've put into this thesis.

To my co-supervisor, Professor John-Bjarne Hansen. While your choice in favorite football teams leaves a lot to be desired, your skills as a researcher and leader of TREC cannot be questioned. You have established an incredible research group where fledgling and more experienced researchers can thrive alongside each other. I have had a great time as a part of TREC, and one of the main reasons has been the great social atmosphere you and Sigrid have created, and your ability to keep everything on track. You are also quite funny.

To all my friends and colleagues in TREC, thank you for making these years so memorable. I am especially grateful to my office buddies, Magnus S. Edvardsen and Birgitte G. Tøndel, your great sense of humor, camaraderie and lack of green fingers always inspired me to work less and relax more. Furthermore, I must thank my other co-authors Line H. Evensen, Kristian Hveem, Maiken E. Gabrielsen, Ben Brumpton, Frits R. Rosendaal, Katalin Veres, Erzsébet Horvath-Puho, Henrik Toft Sørensen, for their contributions. Also, I am grateful to Vegard Skogen and the Research Program for Medical Students at the university, that enabled me to immerse myself in this project during medical school.

Finally, I want to thank all my friends and family for their unwavering support in all my pursuits. To my brothers Snorre, Audun, Knut and Kyrre, and my sister, Arja – you are all equally great. To my mother, Maja-Lisa, you have provided me with emotional and physical shelter throughout my life. You have been a true role model every step of the way and your consistent ability to take credit for anything I do never ceases to amaze me. To my father Egil, who, despite his absence, will always inspire me. Lastly, I am especially grateful to Marita and Anna for their love, support and belief in me.

Lists of papers

The thesis is based on the following studies:

I. **The estimated lifetime risk of Venous Thromboembolism in men and women**
Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK.
Eur J Epidemiol 2022 Vol. 37 Issue 2: 195-203. DOI: 10.1007/s10654-021-00813-w

II. **The Risk of Venous Thromboembolism Attributed to Established Prothrombotic Genotypes**
Evensen LH, Arnesen CAL, Rosendaal FR, Hveem K, Gabrielsen ME, Brumpton BM, Hansen JB, Brækkan SK
Thromb. Haemost. 2022 Vol. 122 Issue 07:1221-1230. DOI:10.1055/a-1698-6717

III. **Proportion of venous thromboembolism attributed to recognized prothrombotic genotypes in men and women**
Arnesen CAL, Hveem K, Gabrielsen ME, Hansen JB, Brækkan SK
Res Pract Thromb Haemost. 2024 Feb 8;8(2):102343.
doi:10.1016/j.rpth.2024.102343

IV. **Body height and risk of venous thromboembolism in men versus women**
Arnesen CAL, Evensen LH, Hveem K, Gabrielsen ME, Hansen JB, Brækkan SK
Manuscript submitted

Sammendrag

Venøs tromboembolisme (VTE) er en vanlig sykdom med alvorlige komplikasjoner som kan oppstå hos menn og kvinner i alle faser av livet. I tidligere studier om VTE-risiko hos menn og kvinner har resultatene variert betydelig. Noen studier har rapportert høyere risiko hos menn, andre hos kvinner, og noen har ikke funnet noen forskjell mellom kjønnene. I tillegg har det blitt foreslått at menn har en høyere iboende risiko for VTE enn kvinner når reproduktive risikofaktorer (graviditet og østrogenbruk) tas i betraktning. Det er kjent at den kjønnsspesifikke risikoen for VTE varierer med alder, så resultatene vil avhenge av aldersfordelingen i studiepopulasjonen, og dette kan forklare de varierende funnene i tidligere studier. Menn har også høyere dødsrater enn kvinner, som kan ha bidratt til overestimering av VTE-risikoen hos menn grunnet høyere konkurrerende risiko for død (CROD). Vi ønsket derfor å studere livstidsrisikoen for VTE hos menn og kvinner når vi tok hensyn til CROD og reproduktive risikofaktorer.

I denne avhandlingen ønsket vi også å undersøke hvorvidt risikofaktorer for VTE påvirket menn og kvinner på ulikt vis. Flere studier har vist at VTE har en sterk arvelig komponent. I de siste tiårene har det blitt oppdaget flere nye enkelt-nukleotid-polymorfismer (SNP-er) assosiert med VTE, men om disse SNP-ene påvirker VTE-risikoen hos menn og kvinner forskjellig er ikke kjent. I tillegg har studier vist en sammenheng mellom kroppshøyde og VTE-risiko. Til tross for at det er en tydelig sammenheng mellom kroppshøyde og VTE-risiko hos menn, har funnene vært varierende hos kvinner. Videre er det foreslått at forskjeller i VTE-risiko for menn sammenliknet med kvinner kan skyldes kroppshøyde, sannsynligvis fordi menn i gjennomsnitt blir høyere enn kvinner.

Derfor undersøkte vi (i) livstidsrisikoen for VTE hos menn og kvinner etter å ha tatt hensyn til CROD og reproduktive risikofaktorer, (ii) estimerte antall VTE-hendelser som kan tilskrives vanlige SNP-er, (iii) estimerte andelen VTE-hendelser hos menn og kvinner som kan tilskrives vanlige SNP-er, og (iv) studerte hvordan kroppshøyde påvirker VTE-risikoen hos menn mot kvinner i ulike aldersgrupper.

Vi fant at livstidsrisikoen for VTE var marginalt høyere hos kvinner enn hos menn når vi tok hensyn til CROD. Da vi i tillegg utelot VTE-hendelser knyttet til reproduktive faktorer hos kvinner, var VTE-risikoen tilnærmet lik hos menn og kvinner, som indikerer at reproduktive faktorers bidrag til livstidsrisikoen hos kvinner er beskjedent. Angående genetisk risiko, fant vi at 45% til 62% av alle VTE-hendelser kunne tilskrives kjente protrombotiske genotyper. Hos menn og kvinner fant vi at henholdsvis 52% og 38% av VTE-ene kunne tilskrives protrombotiske genotyper. Andelen VTE-hendelser som kunne tilskrives genotyper varierte mellom aldersgrupper og var særlig høy blant middelaldrende menn. Økende høyde var en risikofaktor for VTE hos begge kjønn. VTE-risikoen hos menn sammenliknet med kvinner varierte mellom aldersgrupper før justering for kroppshøyde, og kroppshøyde påvirket estimatene betydelig i alle aldersgrupper, noe som antyder at VTE-risikoen i større grad skyldes kroppshøyde hos menn enn hos kvinner.

Summary

Venous thromboembolism (VTE) is a common disease with severe complications that affects men and women at all stages of life. Earlier studies on VTE risk in men and women have yielded conflicting results. Some studies have reported a higher risk in men, others in women and some find no difference at all. It has also been suggested that men have a higher inherent risk of VTE than women when reproductive factors (pregnancy and estrogen use) that increase VTE risk are accounted for. Furthermore, the sex-specific risk of VTE varies with age, so the results are dependent on the age range of the study population, which could explain the varying findings in earlier studies. Men also have higher death rates than women, which may contribute to an overestimation of VTE risk in men due to a higher competing risk of death among men (CROD). Hence, we wanted to investigate the lifetime risk of VTE in men and women when we accounted for the CROD and reproductive risk factors.

This thesis also aimed to investigate whether certain risk factors affected men and women differently. Several studies have shown that VTE has a strong heritable component. In the last few decades, several new single nucleotide polymorphisms (SNPs) associated with VTE have been discovered, but whether these SNPs influence the VTE risk in men and women differently is not known. Additionally, studies have shown an association between body height and VTE risk. However, while there is a clear association between body height and VTE risk in men, the findings have been inconsistent in women. Further, it has been proposed that differences in VTE risk in men versus women could be due to body height, likely due to men's tendency to reach a taller stature.

Therefore, we (i) investigated the lifetime risk of VTE in men and women after accounting for CROD and reproductive risk factors, (ii) estimated the proportion of VTE events that are attributable to common SNPs, (iii) estimated the proportion of events in men and women that can be attributed to these SNPs and (iv) investigated the influence of body height on VTE risk in men and women.

We found that the lifetime risk of VTE was marginally higher in women than in men when we accounted for CROD. Also, when we accounted for events associated with reproductive factors, the VTE risk was essentially similar in men and women, which indicates that reproductive factors contribute modestly to the lifetime risk in women. Regarding the genetic risk, we found that 45% to 62% of all VTE events can be attributed to known prothrombotic genotypes. In men and women, we found that 52% and 38% of VTEs could be attributed to the prothrombotic genotypes. The proportion of VTE events that could be attributed to genotypes varied across age groups and was particularly high among middle-aged men. For body height, we found that taller stature was a risk factor for VTE in men and women. The VTE risk in men versus women varied across age groups, but body height still substantially affected the estimations in all age groups and suggest that VTE risk is mediated through body height to a larger extent in men than in women.

Abbreviations

ARIC	Atherosclerosis Risk in Communities study
AT	Antithrombin
BMI	Body mass index
CHS	Cardiovascular Health Study
CI	Confidence interval
CIF	Cumulative incidence function
COC	Combined oral contraception
CPR number	Central person register number
CROD	Competing risk of death
CRS	Civil Registration system
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CTPA	Computed Tomography Pulmonary Angiogram
CVD	Cardiovascular disease
DCH	Danish Diet, Cancer and Health study
DNA	Deoxyribonucleic acid
DNPR	Danish national patient registry
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
F2	Prothrombin
FVL	Factor V Leiden
GWAS	Genome-wide association study
HLU	Hague, Leiden and Utrecht study
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
HUNT	Trøndelag Health Study
ICD	The International Classification of Diseases
IL-1	Interleukin-1
IR	Incidence Rate
IRR	Incidence rate ratio
KM	Kaplan-Meier
LITE	Longitudinal Investigation of Thromboembolism study
LMWH	Low-molecular-weight Heparin
MEGA	Multiple Environmental and Genetic Assessment of Risk Factors for VTE study
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
OC	Oral contraception
OR	Odds ratio
PAF	Population attributable fraction
PCOS	Polycystic Ovary Syndrome
PE	Pulmonary embolism
Post-PE syndrome	Post-pulmonary embolism syndrome
PPV	Positive predictive value
PTS	Post-thrombotic syndrome
PY	Person-years
REP	Rochester Epidemiology Project
RR	Relative Risk
RRI	Relative risk increase
SAS	Statistical Analysis System
SNP	Single nucleotide polymorphism
STATA	Stata Corporation
TF	Tissue factor
TNF-α	Tumor Necrosis Factor alfa
UNN	University Hospital of North Norway
VTE	Venous thromboembolism

1. Introduction

1.1 Venous thromboembolism

Venous thromboembolism (VTE) is a term combining the conditions deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the formation of a blood clot in the deep veins, most commonly of the large veins of the leg or thigh, but thrombosis can also occur at more unconventional sites, such as in the veins of the upper limbs, as well as in abdominal or cerebral veins (1). After forming, DVT can inhibit the venous circulation, thereby causing common signs and symptoms of DVT, including, swelling, redness and pain in the affected body part (2). PE is mainly caused by a dislodged thrombus that travels with the venous bloodstream to the lungs, where it lodges and impedes the blood flow (3). Signs and symptoms of PE differ vastly from DVT and may be diffuse and unspecific. The most common symptoms include chest pain, coughing, shortness of breath and rapid breathing (3).

One of the first historical examples of VTE caused by sex-specific risk factors and triggers in men and women can be traced back to the 16th century and the British royal families. In 1536, Henry VIII of England (1491-1547) developed DVT due to severe injuries procured from a sports-related horseback-riding incident, and was subsequently bothered with venous ulceration for the rest of his life (4). His grandniece, Mary Queen of Scots (1542-1587) also developed DVT, but under rather different circumstances. In 1567, after being abducted and coerced into a marriage which subsequently forced her to abdicate and then led to her imprisonment, she suffered a miscarriage of twins and developed post-partum venous thrombosis of the left leg (4, 5). Henry treated his leg with pearl dust and garters, while Mary was primarily prescribed cinnamon water, unicorn's horn and baths of wine. While the effect of most of these treatments is questionable, and VTE treatment has evolved considerably in the ensuing centuries, Henry was onto something with the use of garters, and his venous ulcerations is a good example of a common complication of VTE, post-thrombotic syndrome (PTS) (6).

VTE poses a significant threat to health and life. Therefore, efficient treatment and prevention is of critical importance (7). Anticoagulant drugs are highly effective in both respects but leads to an elevated risk of bleeding (8). Heparin was the initial anticoagulant utilized for VTE treatment, with its discovery dating back to 1916 (9). Heparin demonstrated

substantial efficacy, and significantly reduced VTE mortality (10). However, the drug had limitations, including the need for parenteral administration and in-hospital treatment. The advent of the oral anticoagulant warfarin, a vitamin K antagonist, enabled post-hospitalization treatment, and the two anticoagulants complemented each other since warfarin's complete anticoagulant effect typically takes a few days to manifest. Therefore, combining it with heparin at the start of treatment was found to be beneficial, and is nowadays referred to as bridging (9). The next leap in anticoagulant therapy occurred in the mid-90s, when low-molecular-weight heparin (LMWH) was introduced, simplifying anticoagulant treatment through subcutaneous administration, and reduced the necessity for extended hospital stays (11). In the 2000s, another class of anticoagulant drugs, the direct oral anticoagulants (DOACs), emerged, further streamlining VTE treatment. While Warfarin is still the preferred treatment in patients with mechanical valves and antiphospholipid syndrome, DOACs are increasingly supplanting vitamin K antagonists, primarily due to their lower bleeding risk and practical advantages, such as standardized dosing and reduce monitoring requirements (9). Furthermore, recent research has demonstrated the satisfactory safety and efficacy of DOACs in a majority of cancer patients, leading to their growing preference over LMWH in this patient population (12). However, LMWH is still preferred in some patient groups, such as during pregnancy and breastfeeding due to insufficient human safety and efficacy data, and because DOACs and vitamin K antagonists crosses both the placenta and through breastfeeding (13).

The distribution of VTE events has historically been reported to be 2/3 DVT and 1/3 PE with or without DVT (14). However, more recent studies on incidence have demonstrated that the dispersal of VTE is approximately 50/50 between DVT and PE (15, 16). The two conditions often occur at the same time, but symptoms quite often only present clinically at one of the sites. Further, multiple studies indicate that PE can originate from thrombus formation in other places than the deep veins (17-19). For instance, thrombus formation in the right atrium due to atrial fibrillation has been identified through autopsy and echocardiography of PE patients, thereby indicating that PEs may also have a cardiac origin (20, 21). Additionally, acute infections in the lungs are associated with an increased risk of PE, possibly due to coagulation and vasoconstriction induced by local inflammation in the lungs (19, 22). Also, PE may lead to atrial fibrillation through right sided pressure overload or inflammatory cytokines, which suggests a bidirectional relationship between the two conditions (18, 23).

1.2 Epidemiology of venous thromboembolism

VTE occurs in 1-2 per 1000 persons annually in a general population and is the third most common cardiovascular disease after stroke and myocardial infarction (MI) (24). VTE can affect all age groups, sexes, and ethnicities, but it mainly occurs in the elderly, which is reflected by incidence rates (IR) in the elderly superseding the young and middle-aged by 10 to 100-fold (25-27). In the European Union, the number of VTE-related deaths has been estimated to more than 500,000 yearly (28). The largest portion of deaths is caused by undiagnosed PE, which is thought to be responsible for almost 60% of the VTE-related deaths (28).

Several studies have reported an increase in the incidence of VTE in the last decades, mainly due to a rise in PE incidence (25, 26, 29). For instance, in a Danish, nationwide population-based cohort study of all hospital-diagnosed VTEs in Denmark, there was a 20% increase in age- and sex-standardized incidence rates of VTE in the period 2006-2015, mainly due to an increase of almost 80% in PE-incidence (16). The Tromsø study observed a 27% increase in age-adjusted IRs of VTE from 1996 to 2012 (figure 1) (25), and the Worchester study in Massachusetts, US reported an 82% increase in incidence of PE from 1985 to 2009 (26). The reason for the observed increase in incidence is not fully understood, but several explanations have been proposed. Improved detection due to new diagnostic methods with increased sensitivity for PE, such as computed tomographic pulmonary angiography (CTPA) and magnetic resonance imaging (MRI), in addition to increased awareness of VTE in the last decades may partially explain the increasing frequency (30). However, most of the advances in diagnostics originated in the late 90s, and the incidence of comparable diseases like stroke and MI has decreased substantially despite the same improvements in diagnostic methods, while VTE incidence continues to rise (16, 25, 26, 31). Therefore, improved diagnostic detection can only partially explain the increasing incidence.

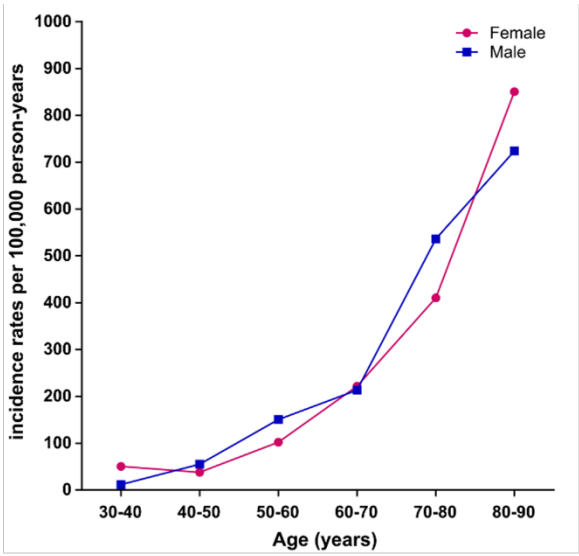


Figure 1. *Age- and sex-specific incidence rates of VTE. The Tromsø Study 1996-2012 (25)*

Furthermore, a considerable rise in VTE-associated risk factors, such as cancer, increasing body mass index (BMI) and age have contributed to the increasing incidence (32).

VTE can lead to both short- and long-term complications (28). Short-term consequences involve the further development of blood clots, early recurrence, and potentially death (33). Studies have reported a 30-day all-cause fatality rate of up to 10%, and a one-year all-cause fatality rate of around 20%, after a VTE event (33, 34). Recent studies have reported a decline in mortality rates after VTE in the past decades, indicating considerable advances in disease management and treatment (35, 36). Furthermore, VTE is associated with long-term and enduring complications such as ***post-thrombotic syndrome***, ***post-pulmonary embolism syndrome*** (post-PE syndrome), and ***late recurrence***. Recurrent thrombosis is relatively common, especially in individuals with unprovoked VTE, and roughly 30% of patients experience recurrences within a decade after their initial VTE diagnosis (33). Major bleeding related to anticoagulant therapy occurs in approximately 10% of patients during the first year following their initial VTE diagnosis (37), and a significant proportion of PE patients experience sudden death as their initial clinical presentation (38). Additionally, PE is estimated to be the primary preventable cause of death in hospitalized patients (39). PTS stands out as the most frequent complication of deep vein thrombosis, affecting a substantial portion of patients with lower limb DVT. Symptoms of PTS vary considerably, and may encompass pain, heaviness, cramps, and persistent swelling of the affected limb. Contributing factors to the development of PTS include sex, obesity, proximal DVT, recurrent DVT, and varicose veins (40). The prognosis of PTS largely hinges on the affected anatomic segment and the time required for vessel strength restoration. PTS can impede patient mobility, diminish their quality of life, and elevate the risk of requiring disability benefits. Post-PE-syndrome is characterized by persistent dyspnea, impaired physical capacity and reduced quality of life (6, 41). One of the most severe manifestations of post PE-syndrome is chronic thromboembolic pulmonary hypertension (CTEPH), which is caused by chronic blockage of major pulmonary arteries and imposes increased strain on the right side of the heart due to abnormally high blood pressure in the arteries (42). Due to the increased arterial pressure, right-sided heart remodeling followed by pulmonary hypertension occurs (43). The incidence of CTEPH is 3% in PE-cases that survives the initial event according to a meta-analysis (44), and has increased in the last decades (45).

The condition tends to be more prevalent in those with unprovoked PE, with most cases identified within the first two years after the initial PE diagnosis.

1.3 Pathophysiology of thrombus formation

Hemostasis is the physiological process that prevents and controls bleeding while maintaining vascular integrity. It involves three main stages: vasoconstriction to reduce blood flow, formation of a temporary "platelet plug" at the injury site, and the coagulation cascade leading to the formation of a stable blood clot. Following clot formation, fibrinolysis dissolves the clot, restoring normal blood flow and tissue repair (46). The pathophysiological development of a venous thrombus is most commonly understood as a disturbance in the hemostatic system, and the overarching disturbances that can lead to such a disturbance is often described with ***Virchow's triad*** (figure 2), developed by the German physician, Rudolf Virchow (47)**.** The triad includes disturbances in the blood flow, and includes changes in blood composition (***hypercoagulability***), changes in blood flow (***stasis***) and changes to the vessel wall (***endothelial dysfunction***).

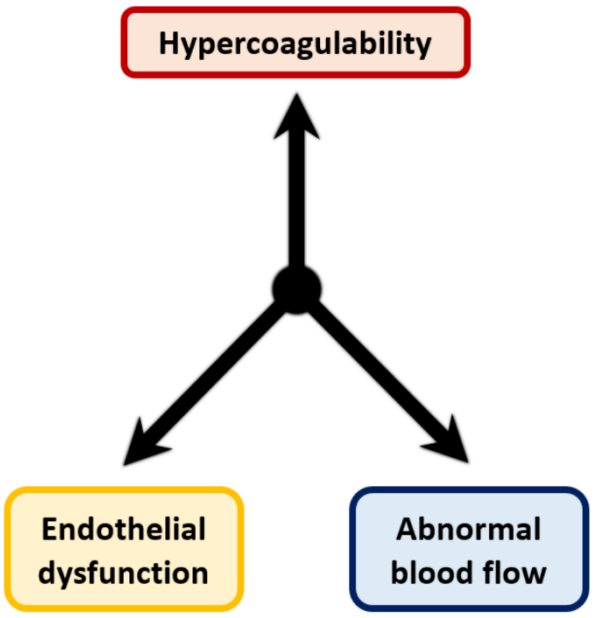


Figure 2. *Virchow's Triad* (47).

Changes in one or more of these categories could overcome the inherent anticoagulant properties of the blood or vessel wall, and activate ***the coagulation cascade***, a stepwise progression of coagulation factor activation that ends with the creation of fibrin, the chief stabilizing element of a thrombus (48, 49). The cascade is initialized through one of the two main pathways, which are known as the intrinsic and extrinsic pathway. The two pathways converge in a common pathway and crescendos with the formation of thrombin. The ***intrinsic pathway*** cascade is triggered by activation of FXII through bacteria, activated platelets or cellular RNA followed by stepwise activation of FXI and FIX which leads to activation of FX and the ***common pathway*** (49). The main player in the ***extrinsic pathway*** cascade is tissue factor

(TF), which constitutively expressed by extravascular tissues/cells and could be triggered by pathophysiological stimuli in monocytes and endothelial cells. (49). TF forms a complex with factor VIIa, which further initiates the activation of FIX, FX and the common pathway. TF is found all over the human body, but especially in vital organs such as the brain, heart, uterus, and lungs (50).

1.4 Risk factors for venous thromboembolism

VTE is a multicausal disease involving combinations of acquired and genetic risk factors but is often triggered by a specific factor. Proposed by Professor Frits Rosendaal, the thrombosis potential model elucidates key concepts in the pathogenesis of VTE and thrombus formation (51). The model proposes that thrombosis arises when a patient accumulates a sufficient set of risk factors and triggers, thereby surpassing the thrombosis threshold. The model is dynamic and allows for diverse interactions between risk factors that could be additive and synergistic, which is particularly useful since the risk of VTE is strongly age-dependent and increases exponentially with age. For example, in children, more risk factors must accumulate for thrombosis to occur than in the middle-aged and the elderly. Thus, individual thrombosis risk varies significantly based on the concurrent presence of risk and trigger factors, the thrombosis-inducing properties of these factors, and their interactions.

There are many possible ways to classify risk factors of VTE, and one common way is to divide it into ***basal risk factors***, ***acquired clinical risk factors*** and ***triggers*** (45). Basal risk factors are usually fairly stable in an individual over time, and their contributions to VTE risk are usually constant and additive. Increasing ***age*** is a basal risk factor that amplifies VTE risk at an exponential rate (31, 52). ***Increased body height*** (53-57) also increases VTE risk substantially. Several ***genetic risk factors*** are associated with increased risk of VTE, and understanding of the role of genetic risk factors and VTE is a field that is still in rapid development (45, 58-61). Acquired clinical risk factors are factors that might present themselves throughout a lifespan and affects the risk of VTE. Examples are ***obesity*** (62-64) and ***medical conditions*** (e.g. cancer and CVD) (65-68)***.*** Triggers are transient factors or conditions that can be classified as acute or subacute. Acute triggers are events or factors that lead to an immediate elevation in VTE risk,

that lasts for a short time. An example of an acute trigger is a bone fracture, that consequently could lead to other acute triggers like immobilization and surgery, that exponentially increases the risk of VTE (69). Subacute triggers are conditions that leads to a persistent elevation in the risk of VTE for the duration of the trigger's effect. An example is pregnancy, where the risk of VTE steadily increases throughout the pregnancy and in the following 6 to 12 weeks (postpartum period) (70).

Obesity is the strongest lifestyle risk factor, and 10-30% of all VTEs can be attributed to obesity (32, 71). Compared to lean persons, obese people have 2-3 times the risk of a first time VTE (62, 72, 73). The mechanisms behind the association between obesity and VTE are not fully understood. However, unlike diseases caused by arterial thrombi, like MI and ischemic stroke, the association with VTE is not explained by classic atherosclerotic risk factors associated with obesity, such as high blood pressure, diabetes and hypercholesteremia (68, 73). Therefore, several hypotheses have been suggested. Studies have found that fatty tissue releases proinflammatory proteins like IL-6 and TNF-alfa, and increased amounts of fatty tissue could lead to chronic inflammation. In addition, fatty tissue also releases adipokines like plasminogen activator inhibitor-1, that inhibits fibrinolysis and increases the risk of VTE (74-76). Additionally, increased intra-abdominal pressure leading to venous stasis could increase the risk of VTE in obese individuals (45).

Several medical conditions are linked to VTE, including but not limited to atrial fibrillation, chronic kidney disease, congestive heart failure, acute infections, ischemic stroke, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome (45). The most important medical risk factor of VTE is ***cancer***, which is associated with a 4- to 7-fold increase in VTE risk, and approximately 20-30% of all VTE cases are related to cancer (66). The risk of thrombosis in cancer patients is highly heterogenous, and the annual incidence varies from 0.5% to 20% depending on both the cancer type and treatment (65).

A common, and well-established acute and transient trigger of VTE is ***surgery***, and historically, VTE was regarded as a complication of surgical interventions (77). For surgery, the risk estimates ranges from 6- to 22-fold based on circumstances like surgery type, basal risk factors, and postoperative complications (78). The surgery types with the highest thrombogenic risk are orthopedic surgery, vascular interventions and neurosurgical

procedures. Therefore, most VTE risk assessment scores for use of anticoagulant prophylaxis in individuals undergoing surgery are based on both patient characteristics and type of intervention (79, 80). Another important acute trigger of VTE is ***hospitalization***, and 40-60% of all VTE events are associated with being institutionalized (70). Studies have indicated that the VTE incidence in hospitalized individuals is 20-100 times higher compared to the general population (70, 81). Additionally, hospitalization is frequently related with continued immobilization, which further increases the risk of VTE (82). The link between hospitalization and several other triggers of VTE further underlines the multifactorial nature of VTE (70, 82).

Subacute triggers are associated with a less dramatic, but more persistent elevation of VTE risk over time than the acute triggers. Several studies have found associations between high concentrations of biomarkers of ***inflammation*** and elevated risk of VTE (45). In addition, ***fluctuations in hormone levels*** are associated with increased risk of VTE and will be discussed below (45).

Men and women are usually subject to the same risk factors for VTE, with some notable exceptions. For women, the most common sex-specific risk factors are associated with ***female reproduction*** and ***hormonal influence*** during their fertile lifespan and is strongly associated with ***estrogen*** (figure 3) (83). Estrogen has comprehensive effects on hemostasis and thrombus generation. It is associated with platelet activation and aggregation, possibly through increase of von Willebrand factor levels, which is central in these mechanisms (84). Further, estrogen leads to thrombin

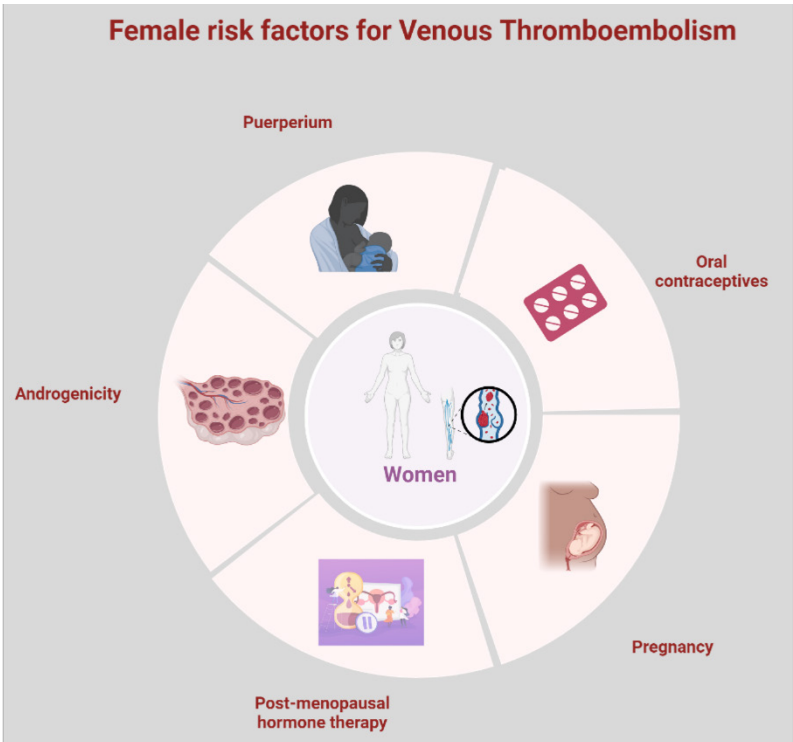


Figure 3. *Female-specific risk factors for venous thromboembolism (83)*

generation and fibrin clot formation through increase of coagulation factor levels, a reduction of anticoagulant proteins levels (antithrombin and Protein S), and decreased potency of the anticoagulant effect of activated protein C (85-87). Estrogen's effect on VTE risk regardless of birth sex is supported by studies on transwomen undergoing gender-affirming hormone therapy, where an increased risk of both venous and arterial thrombosis compared to cis-men has been reported (88).

The first hormonal contraception device was the combined ***oral contraception*** pill (COC) Enovid/Enavid, which was introduced in 1960, and consisted of 150 micrograms of estrogen and 10 micrograms of the synthetic gestagen, Norethisterone (89). The first reported case of VTE associated with Enavid was reported the following year (90). Even at the time, it was theorized that estrogen led to increased risk of VTE, and the dose was gradually lowered. Hence, since the 1970s, the amount of estrogen in a COC has rarely exceeded 20-30 micrograms (91). Despite the reduction in estrogen dose, and a marked reduction in COC-related VTE risk (92, 93), numerous large studies have consistently found a transient 2- to 4-fold increase in risk of VTE in COC users compared to non-users (91). Additionally, the risk of VTE is dependent on the gestagen component of the COC. COCs are often inconsequentially grouped into generations based on when they were introduced, and an example based on when a type of gestagen was introduced can be found in figure 4 (91).

Generation	Type of Gestagen
1st	Norethindrone Lynestrenol
2nd	Norgestrel Levonorgestrel
3rd	Desogestrel Gestodene Norgestimate Drospirenone

Figure 4. *Types of gestagen by generation (91)*

The contraceptive effect is largely similar in all COCs, but the side effects and risk of VTE varies. Of note, studies have indicated that users of third-generation COCs have a higher risk of VTE than second-generation users due to increased resistance to activated protein C (89, 91). In a Danish national cohort study comprised of women aged 15-49 years, Lidegaard et al. concluded that non-users of oral contraceptives (OC) had a risk of 3.01/10 000 person years, compared to 6.29/10 000 person years in current users, thus implying a more than two-fold increased risk of VTE in women using OC (93). The study found that risk of VTE was only increased in women using combined OCs comprised of estrogen and synthetic gestagens, and not in women using pills solely consisting of progestogens or hormone releasing intrauterine

devices. That progestin-only pills do not increase VTE risk has been supported by later studies (92, 94). In 2014, a comprehensive meta-analysis of VTE risk and COC use was published (91). Overall, the study found that all COC users had at least a 2-fold increase in VTE risk compared to non-users, and the risk surged with increasing estrogen dose. The lowest risk of VTE among COC users compared to non-users was found among levonorgestrel (RR: 2.2, 95% confidence interval [CI]: 1.3-3.6) and gestodene users (RR: 2.2, 95% CI: 1.4-3.2), while the users of drospirenone (RR: 3.9) and desogestrel (RR: 3.4) had the highest risks compared to non-users, further establishing the prothrombotic and procoagulant effect of COCs. In addition to COCs, women experiencing menopause could have an increased risk of VTE due to exposure to estrogen through hormone replacement therapy (HRT) During menopause, estrogen levels fall considerably, and could subsequently lead to hot flushes, night sweats, loss of bone density and vaginal discomfort (95). Roughly 1-2 out of 10 experiences such complications, and receive HRT. The risk varies, but the increased risk is roughly 1.6-3-fold compared to non-users (95, 96).

Despite the evidence that supports the association between exogenous estrogen usage and increased risk of VTE there is conflicting findings on whether endogenous estrogen levels increase risk of VTE in women. A paper based on the Copenhagen City Heart Study cohort, found no increase in VTE risk in pre- or postmenopausal women with high vs. low estrogen levels (97). However, the median time from the drawing of blood samples to event was 17.6 years. Conversely, the MEGA case-control study, which had a shorter time from event to blood sampling, found that estrogen was associated with VTE risk in the highest quartile compared to the lowest (OR: 1.6, 95% CI: 1.0-2.5) (98).

In pregnant women, the risk of VTE is at least four times higher than the risk in nonpregnant, fertile women (99). During pregnancy, the risk increases throughout, and peaks in the third trimester. Furthermore, the highest risk has been observed in the first week after delivery (100), followed by a gradual decline until week 6, when it is no longer significantly increased compared to the general population. There are several pathophysiological

components that contribute to the increased VTE risk. In the first trimester, the increased risk of VTE is caused by hypercoagulability due to hormonal changes like estrogen increase, which is known to affect coagulation factor levels (101). Additionally, in the latter part of the pregnancy, the growing uterus and increased weight leads to venous stasis due to physical pressure on the pelvic veins (figure 5) (100). In addition to pregnancy, polycystic ovary syndrome (PCOS) is a condition where endogenous sex hormones are an important contributor (88, 102). It is defined by androgen excess (acne, alopecia), ovulatory dysfunction and polycystic ovarian morphology. In a meta-analysis, the risk of VTE was estimated to be 1.5-2 fold higher in individuals with PCOS compared to women without PCOS (102).

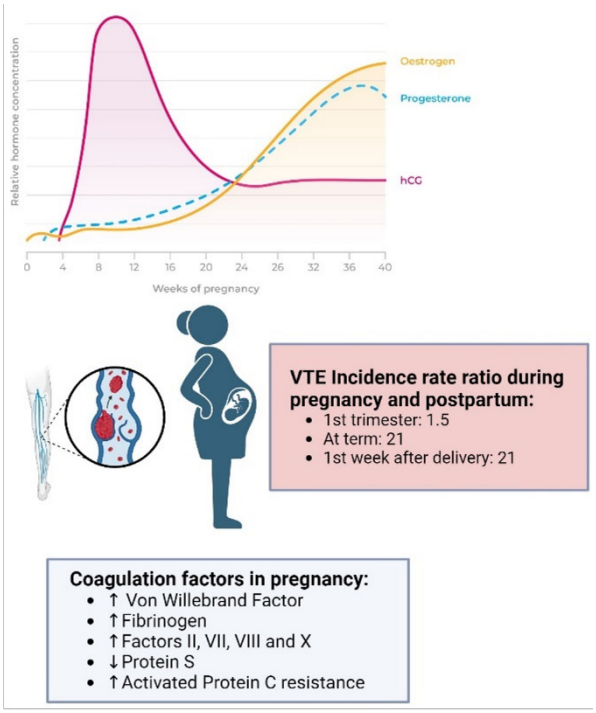


Figure 5. *Patophysiological components that contribute to increased VTE risk during pregnancy and the postpartum period* (100).

In men, there are fewer sex-specific risk factors that increase risk. Exogenous sex hormones have been associated with increased risk of VTE in men, but the estimates for exogenous testosterone use have not been as robust as those observed for estrogen in women (45). In individuals with increased endogenous testosterone levels, there is limited data, but neither the Tromsø nor the Copenhagen City Heart Study found an increased VTE risk in men with high testosterone levels (97, 103). However, the prothrombotic effect of estrogen is also clear in men born with a biologically male sex, undergoing gender-affirming therapy (104, 105).

1.5 Incidence and lifetime risk of first-time VTE in men and women

A plethora of studies have documented an exponential increase in VTE incidence with increasing age (figure 6) (14, 25, 29, 106). While the risk per decade has been calculated to increase by 1.8- to 2.5-fold (67), the risk in individuals aged >80 years is more than 100-fold the risk of individuals aged <15 years (29). The previous literature on VTE risk in men and women has been inconsistent. Some studies have found a higher risk of VTE in men than in women, (14, 29, 107), while others have shown a higher risk in women than in men (26, 37, 108). Furthermore, some studies have found no difference in sex-specific risk of VTE at all (109).

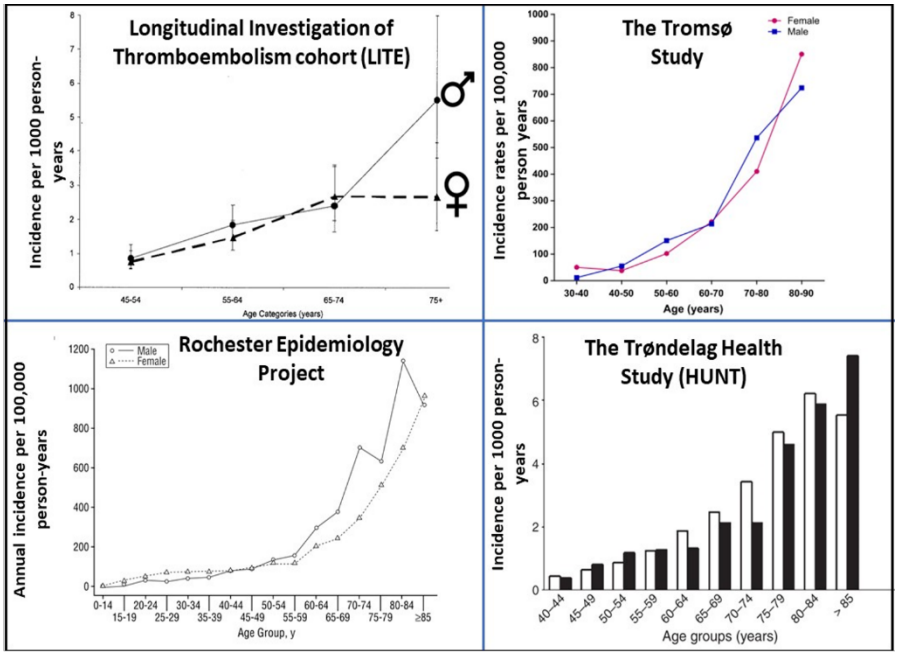


Figure 6. *Lifetime risk of VTE in four different cohorts (14, 25, 29, 106)*

In younger age-groups (<50 years), most studies have reported a higher incidence of VTE in women (25, 27, 110). For example, in individuals aged 20-49, the Trøndelag Health study (HUNT) reported a 1.6-fold higher risk of VTE in women compared to men (27). In the Tromsø study, women aged 30-50 years had a 1.1-fold increased risk of VTE compared to men (25). A Dutch population study in the municipalities of Hague, Leiden and Utrecht (HLU) estimated a 1.6-fold higher risk in premenopausal women compared to men (110). The elevated VTE incidence in younger women compared to men is largely explained by female-related risk factors, like oral contraceptives and pregnancy (93). Using the Multiple Environmental and Genetic Assessment of Risk Factor for venous thrombosis case-control study (MEGA study), Roach and colleagues showed that the risk of a first VTE was 2-fold higher in men than in women who had not been exposed to reproductive risk factors for VTE (oral contraceptive use,

post-menopausal hormone therapy or pregnancy) (111). Furthermore, the women aged 18-50 years who were exposed to reproductive risk factors had 2- to 6 times the risk of experiencing a VTE compared to men in the same age group. These findings support the notion that the intrinsic risk of VTE might be higher in men than in women once reproductive risk factors are accounted for. This theory is further supported by the observed increased risk of recurrence reported in men (112, 113). However, the MEGA study consisted of VTE patients that had survived the initial phase of anticoagulant therapy, and the case-control design did not permit the calculation of absolute risk differences.

Among the middle-aged (50-74 years), most studies have reported a higher incidence of VTE in men than in women. The Rochester Epidemiology Project (REP), an American, population-based cohort study, reported a 1.6-fold higher incidence in men compared to women (29), while the HLU, HUNT and Tromsø studies reported a 1.4-, 1.3- and 1.2-fold higher incidence in men, respectively (25, 27, 110). In the elderly (≥75 years), the incidence rates of VTE increases exponentially in both men and women. Both the HUNT and Tromsø study reported similar incidence rates between the sexes (25, 27). However, the REP study reported a 1.2-fold higher incidence in men (29), and the Longitudinal Investigation of Thromboembolism (LITE) study estimated that the risk of VTE in elderly men is twice what the risk is in elderly women (107). Taken together, the existing literature on the sex-specific risk of VTE in men and women indicates that women have a higher risk of VTE in the young, mostly due to reproductive risk factors, whereas the risk is higher in men among the middle-aged and essentially similar among the elderly. Therefore, the inconsistent findings in previous studies on the risk of VTE in men and women could be explained by differences in the age-ranges of the populations under study since the sex-specific risk in men and women fluctuates considerably with age (52, 114).

While the overall incidence rates of VTE in men and women has been studied in numerous studies consisting of populations of varying age-range, the lifetime risk has rarely been estimated. Of note, since most VTE events occur after the age of 60, the population that has the highest risk of VTE also has increased risk of competing events, which may impact risk estimates through an overestimation of risk in traditional survival analysis. A central assumption in traditional survival analysis is the concept of non-informative/independent censoring, which assumes that censoring occurs randomly, and is unrelated to the outcome of interest. In other words, the uncensored individuals who are still under follow-up should be representative of the survival risk of censored individuals (115). However, some reasons for censoring does affect an individual's risk of experiencing an event, and the competing event that has the strongest impact on the risk of VTE is ***the competing risk of death***. Death would change the risk of an event, for example VTE, to zero. Therefore, the censoring would be informative, and it would subsequently lead to an overestimation of the incidence in groups affected by the competing risk of death. Naturally, the risk of death on a population level increases with age, and length of follow-up. In men and women, the lifetime risk would therefore be overestimated with age in both sexes, but the comparison between the two groups would only be compromised if the competing risk is more substantial in either men or women. International death rates show that men have a higher death rate than women in all age groups (116). Norwegian death rates show the same pattern (figure 7) (117).

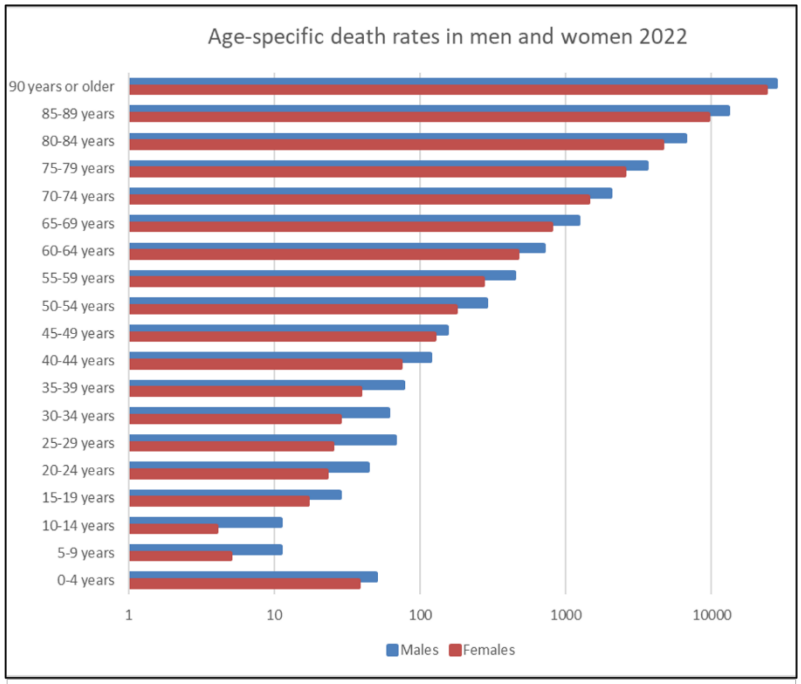


Figure 7. *Age-specific death rates in Norwegian men and women in 2022 (117).*

In a review article by Engbers et al., the lifetime risk of VTE was estimated to be 15% (118). However, this study did not account for the competing risk of death. We know of only one study that has examined the lifetime risk of VTE in men and women while accounting for the competing risk of death. The study used data from two, large prospective cohort studies, the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS) and consisted of 19,599 participants aged ≥45 years who were followed up from date of inclusion to either age 85 or end of follow-up. The follow up-period was from 1987-2011 in ARIC and 1989-2001 in CHS, and the estimated overall lifetime risk was 8.1%. In men, the risk was 7.7%, while in women, the risk was 8.4% (119). The results indicate that women might have a slightly higher lifetime risk. However, the study had some limitations. First, the study population did not include younger participants, an age range where women have a considerably higher risk of VTE than men (27, 29, 120), and therefore the lifetime risk estimates could be somewhat underestimated in women. Second, the study only calculated the risk up to age 85, therefore the lifetime risk is potentially underestimated, and any difference in risk among men and women in individuals ≥85 years would not be included in the estimated lifetime risk. An estimate of the overall lifetime risk of VTE in men and women in a population that included the entire lifespan was therefore of significant interest.

1.6 Genetic risk factors and VTE in men and women

The first report of a family with a clearly recognized hereditary risk of thrombosis was made by the Norwegian doctor Olav Egeberg in 1965. He identified an antithrombin (AT) deficiency in a Northern Norwegian family from the island of Skjervøy (51, 121). Now, we know that individuals with an AT deficiency have a more than 10-fold increased risk of VTE, but less than 0.2% of the general population have the deficiency. In the ensuing decades, several other rare defects were uncovered, such as protein C and S deficiencies, which are associated with a 5- and 7-fold increase in the risk of VTE, respectively. Nonetheless, these defects are only found in less than 0.5% of the population, and while potent when present, they only account for a small percentage of the VTE events in the population (122). Additionally, family and twin studies have suggested that the hereditary component for VTE is strong, with a reported heritability of up to 60% (123), which suggests that VTE heritability is multifactorial and complex (124).

Since the early 90s, and the advent of the mapping of the human genome, several new heritable risk factors, or single nucleotide polymorphisms (SNPs) have been found to be associated with an increased risk of VTE (60, 124, 125). Some genetic variants, such as factor V Leiden (FVL) (Relative risk increase [RRI]: 2- to 3-fold, prevalence: 2-5%), prothrombin G20210A (RRI: 3- to 4-fold, prevalence: 2%), and non-O blood groups (RRI: 1.5-fold, prevalence: 60%), are associated with a significantly increased risk of VTE (122, 126, 127). However, there are hundreds of SNPs associated with VTE, and most of the effect estimates are rather small (60, 128). Therefore, the combined effect of multiple SNPs on the risk of VTE is important to investigate.

The MEGA and Leiden Tromphophilia studies examined the performance of a polygenetic risk score based on 31 SNPs known to be associated with VTE and compared it with a parsimonious 5-SNP score consisting of the SNPs with the strongest association to VTE (129). This 5-SNP model had similar results to the 31-SNP model, thereby indicating that a large proportion of the genetic risk is attributable to a small amount of prothrombotic SNPs. However, the analysis was conducted in case control populations with no participants older than 70 years. Furthermore, an American case-control study calculated the individual and

cumulative population attributable fraction (PAF) of FVL, prothrombin (F2) and non-O blood groups, and found a cumulative PAF of 40% (126). In genetic research on VTE, PAF is a measure that is used to assess the proportion of VTE that are attributable to a risk factor. The PAF estimate is dependent on both prevalence and the risk estimate and can assess individual and cumulative contributions on a population level. Hence, the case-control study indicated that 40% of all VTE events were attributable to FVL, F2 and non-O genetic variants. However, since most studies that have investigated prothrombotic genotypes are case-control-studies, the results could be overestimated. Additionally, the FVL genotype is known to lead to a higher risk of DVT than PE, known as the "FVL paradox". However, little is known about whether other prothrombotic genotypes could have similar effects (130). Previous studies have also found that individuals with prothrombotic genotypes who experience a VTE are much more likely to have their first event at young age, rather than later in life (118, 131). However, the number of genotypes investigated in these studies were limited, and their effects in different age groups have not been extensively studied in population-derived cohort studies.

Multiple studies have investigated whether the association between VTE and genetic risk factors vary in men and women (120, 122, 126, 132). Using the Swedish Multi-generation register, Zöller and colleagues investigated the heritability of VTE in the general Swedish population (132). They found that the genetic heritability of VTE was 47% for men and 40% for women. The sex-difference in heritability was higher for unprovoked VTE (51% in men and 30% in women). These studies suggest that genetic factors may contribute differently to VTE risk in men and women. Moreover, data from the MEGA case-control study showed that the strength and prevalence of these SNPs was similar in male and female controls. The individual PAFs in men and women were 10% and 8% for FVL, 4% and 3% for prothrombin, and 39% and 35% for non-O blood group (120). However, the impact of prothrombotic variants has not been assessed in a population-based case-cohort with a wider age range, which would enable the calculation of absolute risk of VTE for each individual SNP in the general population. Furthermore, the impact of newly discovered SNPs and the combination of several prothrombotic SNPs on the risk of VTE in the general population, and men and women has not been broadly studied. Further the proportion of VTEs that can be attributed to recognized prothrombotic genotypes has not been determined in the general population or in men and women of different ages.

1.7 Body height and risk of VTE in men and women

Taller stature is a recognized risk factor of both first-time and recurrent VTE in the general population (53, 133-135). The causal relationship between body height and VTE has been confirmed through a mendelian randomization study that found that single-nucleotide polymorphisms associated with greater height were related to VTE (57), and further consolidated by a co-sibling study that found that increased body height was associated with increased VTE risk, regardless of common environmental and genetic risk factors (56). However, the association between increasing body height and VTE risk in men and women has yielded some ambiguous results. All studies report a consistent relationship between increasing height and VTE risk in men (53, 54, 56, 63), but the relationship has not been as consistent in women (53, 54). A Dutch case-control study used 166-170 cm as a reference group and found a consistent dose-response relationship between taller stature and VTE risk in men. The VTE odds ratio (OR) risk by body height peaked in the tallest height category (>200 cm, OR: 3.8). However, for women the risk of VTE barely increased with increasing body height and peaked in the tallest height category (>185 cm, OR: 1.5) (54). A previous study from the Tromsø cohort reported a similar trend, with a hazard ratio (HR) per 10 cm increase in body height of 1.34 in men, but only 1.13 in women (53). All these studies had a limited number of participants in the highest and lowest height categories. Therefore, the inconsistent risk estimates in women could be explained by lack of power in taller height groups. Conversely, the Iowa Women's Health study found a 1.8-fold higher risk of VTE in taller women (136), and a Swedish registry-based study including over 1 million men and 1 million women reported a similar association between taller stature and VTE in both sexes (56).

The more consistent association between body height and risk of VTE detected in men could be due to men's tendency to reach a taller stature than women. This possibility has been further explored in The Danish Diet, Cancer and Health (DCH) cohort conducted by Severinsen et al., which consisted of a middle-aged population aged 45-70 years at baseline. The study found that an increased incidence rate ratio (IRR) of VTE in men versus women (IRR:1.55) was eliminated when accounting for differences in body height (IRR: 0.82) (55), thereby indicating that body height could play an important part in understanding the VTE risk profiles of men and women. However, the VTE risk in men versus women after adjustment for body height

has not been explored in an unselected population consisting of all age groups. This is of considerable interest, since body height could play a major role for the risk of VTE in men versus women across age groups (45, 52).

2. Aims of the thesis

The specific aims of this thesis were:

I. To estimate the lifetime risk of VTE in men and women taking the competing risk of death into account in a nationwide cohort.

II. To estimate the proportion of VTEs in the population that could be attributed to established prothrombotic genotypes using a population-based case-cohort.

III. To estimate the individual and cumulative PAF of established prothrombotic SNPs in men and women, and to estimate the cumulative PAF in men and women across age groups in a population-based case-cohort.

IV. To investigate the risk of VTE according to body height in men and women in a large population-based cohort, and to investigate the risk of VTE in men versus women after adjustment for body height in young, middle-aged and elderly individuals.

3. Methods

3.1 Study populations

3.1.1 The Tromsø Study

The Tromsø study is an ongoing, single center prospective population-based study with repeated health surveys of the inhabitants of the municipality of Tromsø, in Northern Norway (137). In total, seven surveys (Tromsø 1-7) have been conducted. The first, Tromsø 1 was conducted in 1974, and bore the name The Tromsø Heart Study, and aimed to investigate arterial CVD. Since then, the focus of the Tromsø Study has expanded considerably, and at present, it covers a broad spectrum of diseases and conditions. Additional surveys were conducted in 1979-80, 1986-87, 1994-95, 2001-02, 2007-08 and 2015-16. In all Tromsø surveys, baseline information was collected through self-administered questionnaires, non-fasting blood samples and physical examination performed by trained personnel. The study's greatest strengths are its longitudinal design, long-term follow-up of patients, high attendance rates, repeated measurements and single center follow-up.

The study population for papers II-IV included surveys 4-7 of the Tromsø Study (137, 138). In 1994-95, all inhabitants of the municipality of Tromsø aged >24 years were invited to participate in the fourth survey of the Tromsø study. The response rate was high (77%) and 27,158 individuals participated. In 2001, Tromsø 5 was conducted, and 8,130 individuals aged 30-89 participated (79%). In 2007-08, Troms 6 included 12,984 participants aged 30-87 years (66%), and in 2015-16, Tromsø 7 included 21,083 participants aged 40-99 years (65%). Overall, almost 40,000 individuals participated in the four surveys, and more than 7000 participated in three or more surveys.

3.1.2 The Trøndelag Health Study

The Trøndelag Health study was initiated in 1984-86, and it's initial aim was to investigated hypertension, diabetes, tuberculosis and quality of life (139). Since then, the scope of the study has expanded considerably. To date, four surveys have been carried out. HUNT1-3 included only inhabitants of the former Nord-Trøndelag county, while HUNT4 included the population of Sør-Trøndelag county. The HUNT2 survey was conducted in 1995-97 and all inhabitants of the Nord-Trøndelag county aged >19 years were invited to participate. In total, 65,228

individuals (69%) participated. The HUNT3 survey was conducted in 2006-08 and included 50,800 participants (54%) aged >19 years. Baseline information was obtained from physical examinations, blood samples and self-administered questionnaires.

3.1.3 The Danish population

Denmark has a government–funded, tax-supported welfare system for the entire Danish population, ensuring free and equal access to education and medical care for all residents. The Danish Civil Registration System (CRS) assigns all Danish residents a unique 10-digit personal identifier (CPR number) upon birth or immigration. This number is used in all Danish registries, thereby enabling record linkage to up-to-date individual level data across all Danish government-maintained nationwide registries, with almost complete long-term follow-up (140). The Danish National Patient Registry (DNPR) is linked to the CRS and contains data on more than 99% of all inpatient stays and outpatient visits to Danish hospitals. Since 1995, every hospitalization or outpatient visit has been recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses coded according to ICD-10 (141).

3.1.4 Exposure measurements

Selection of SNPs and genotyping

For both studies, genotyping was performed for seventeen SNPs with recognized association with VTE risk (125, 128). The Tromsø sample was genotyped using the Sequenom and the TaqMan platforms. The HUNT sample was genotyped using the Illumina HumanCoreExome array. Individuals were classified as carriers (≥1 risk allele) or noncarriers (0 risk alleles), and no differentiation was made between hetero- and homozygous carriers in the analyses. For the SNPs rs4524 (F5), rs2036914 (F11), rs1801020 (F12), rs1039084 (STXBP5), and rs1613662 (GP6), the major allele was defined as the risk allele. (125, 128). For the rs8176719 SNP in the ABO gene, the G allele tags non-O blood type (risk group), while homozygous carriers for deletion at this site are phenotyped as blood type O (reference group) (142).

Measurement of body height and confounders

Baseline information was obtained from physical examinations, blood samples and self-administered questionnaires in both cohorts. Measurement of body height and weight was conducted at the physical examination with participants wearing light clothes and no shoes. In Tromsø 4 and HUNT2, height was measured to nearest centimeter (cm) and weight was measured to the nearest half kilogram (kg), while Tromsø 5-7 and HUNT3 measured height to the nearest millimeter and weight to the nearest hectogram. BMI was calculated as weight in kg divided by the square of height in meters (kg m-2). Information on arterial cardiovascular disease (CVD; myocardial infarction, stroke, and angina) and smoking was collected via self-report questionnaires.

3.2 Outcome measurement

3.2.1 Venous thromboembolism

In paper I, the entire population of Denmark in January 1st, 1995 served as a source cohort. We categorized the cohort according to sex and age groups, and follow-up time was the period January 1, 1995, through December 31, 2016. We used data from the DNPR to identify all inpatients and outpatients with a first-lifetime primary or secondary diagnosis of DVT, PE, splanchnic vein thrombosis or cerebral vein thrombosis. We used ICD-10 codes to identify all in- and outpatients with a diagnosis of DVT or PE in this period (141).

In papers II-IV, we used data from the Tromsø study, which started a VTE registry in 1994. All possible VTE events from January 1st, 1994 through December 31st, 2012 papers II and III, and January 1st, 1994 through December 31st 2020 in paper IV were identified and validated by trained personnel using the radiology procedure registry, hospital discharge diagnosis registry and the autopsy registry at the University Hospital of North Norway (UNN), Tromsø. UNN Tromsø is the sole provider of all VTE related health care and diagnostic radiology procedures for VTE in the area. The discharge diagnosis codes used were the International Classification of Diseases (ICD)-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994-98, and the ICD-10 codes I26, I80, I81, I82, I67.6, O22.3, O22.5, O87.1 and O87.3 for the period 1999-2020. A diagnosis of VTE was verified and recorded when objective

confirmation tests, such as venography, spiral computed tomography, compression ultrasonography, pulmonary angiography, prefusion-ventilation scan or autopsy were combined with the presence of clinical signs and symptoms. For cases derived from the autopsy registry, a VTE event was only recorded when the autopsy-record indicated PE as the sole cause of death or as a significant contributing cause of death. Patients with concurrent DVT and PE were registered as having PE. Recurrent episodes of VTE were identified and validated using the same criteria as described above for first lifetime VTE events.

In the HUNT Study, used in papers II-IV, VTE events were identified by searching the discharge diagnosis registry and the radiology procedure registry at two local hospitals (Levanger and Namsos) and the discharge diagnosis registry at the tertiary-care center in the region, St. Olavs Hospital in Trondheim. The medical records were reviewed by health-care personnel, and the diagnosis criteria for VTE were symptomatic DVT or PE confirmed by a radiological procedure (venography, duplex ultrasound and Doppler ultrasound). VTEs were identified by hospital discharge codes; ICD-9 codes 415.x, 451.x, 452, 453.x, 325, 362.3, 433, 557.0, 634–638 (with decimals 6 and 7), 639.6, 639.8, 639.9, 671.x, 673.x, 674, and 997.2, and ICD-10 codes I26.x, I80.x, I81, I82.x, I 63.6, I67.6, K55, H34.8, O08.x, O22.x, O87.x, and O88.x. Two physicians reviewed and validated potential VTE cases. DVT cases and PEs were objectively confirmed by radiological procedures (27).

All events were classified as either PE (with or without DVT) or isolated DVT and as provoked or unprovoked based on the presence of provoking factors at the time of diagnosis. In the Tromsø Study, the VTE events were classified as provoked if one or more of the following provoking factors were present: surgery, trauma or acute medical conditions (acute myocardial infarction, acute ischemic stroke, or acute infection) within 8 weeks prior to the event, immobilization (bed rest >3 days or confinement to wheelchair within the last 8 weeks, or long-distance travel ≥4 h within the last 14 days), active cancer at the time of VTE diagnosis, or other factors specifically described as provoking by a physician in the medical record (e.g., intravascular catheter). In the HUNT Study, an event was labeled as provoked if one or more of the following factors were present: trauma or surgery, cancer (active malignancy at the time of the event or within 6 months after the event), marked immobilization (paresis, paralysis, prolonged bedrest due to acute medical illness, or travel >8 hours) within the previous 3

months, pregnancy or puerperium at the time of the event, or use of oral contraceptives at the time of the event or up to one month prior to the event. Strengths for both the Tromsø and HUNT studies are: Clearly defined geographical areas, feasible follow-up of disease occurrence and outcome due to few hospitals in the region.

3.3 Statistical Analysis

Estimated lifetime risk and competing risk of death (Paper I)

Paper I was a nationwide cohort study where we calculated the cumulative incidence of VTE in men and women when accounting for the competing risk of death. Person-time of follow-up accrued from inclusion in the cohort until the date of an incident VTE, emigration from Denmark, death, or end of the study period (Dec 31, 2016), whichever occurred first. To estimate IRs of VTE and death, the population was divided into five-year age groups ranging from 0-4 to 100+ years, and age was used as time scale. Additionally, individuals contributed person-time to different age groups as they grew older during the study period. These IRs were expressed as number of events per 1000 person-years (PY) at risk. Since VTE is strongly associated with increasing age, and men have a higher mortality risk than women, the cumulative incidence could be more overestimated in men than in women (143, 144). Therefore, cumulative incidence curves with and without death as a competing event were estimated using age as the time scale. Cumulative incidence with death as a censoring event was estimated using the complement of the Kaplan–Meier product limit estimator (1-KM), while the cumulative incidence estimates with death as a competing event was calculated using the cumulative incidence function (CIF), developed by Fine and Gray (145). The estimated lifetime risk was defined as the CIF-estimate at age 100. Additionally, since the incidence of VTE has increased in the last decades, we conducted sensitivity analyses to study whether potential birth cohort effects differed in men and women.

Proportion of VTE attributable to prothrombotic genotypes (Papers II-III)

Papers II and III were case-cohort studies where we investigated the proportion of VTE events attributable to known, common prothrombotic genotypes in the general population, and in

men and women, respectively. We calculated hazard ratios with 95% CIs using Cox regression models, with non-carriers (0 risk alleles) serving as the reference group. Age served as time scale. The entry time was age at inclusion and exit time was age at VTE/ censoring, and the model was adjusted for BMI. To ensure that the proportional hazards assumption was not violated, we used Schoenfeld residuals.

The population attributable fraction (PAF) was calculated individually for each SNP with the formula $\frac{p(HR-1)}{p(HR-1)+1}$, where *p* represents the prevalence of carriers in the population (146). Additionally, we created a cumulative 6-SNP PAF model based on the highest individual PAF estimates. Additionally, prothrombin was added due to its considerable HR. The model was created for the general population and men and women. We also calculated the cumulative PAF of the 6-SNP model according to separate age groups (<70 years and ≥70 years) in the total population and according to ≤50, 50-74 and ≥75 years in men and women.

Body height and risk of VTE (Paper IV)

Paper IV was a population-based cohort study where we investigated the risk of VTE according to body height in men and women and assessed VTE risk in men versus women after adjustment for body height in the young, middle-aged and the elderly. Cox-proportional hazards regression models were used to estimate sex-specific HR with 95% CIs for VTE in men and women according to 5-cm body height categories before and after adjustment for BMI. The 166-170 cm category was used as reference group for both sexes. In addition, we also estimated VTE risk per 10 cm increase in body height in men and women. Next, we split the population into age categories, and estimated the VTE risk in men versus women in the age groups 19-49, 50-74 and ≥75 years before and after adjustment for height. Furthermore, we estimated the hazard ratios when taking the competing risk of death into account, and the HRs of unprovoked and provoked VTE for every age category and adjusted for body height.

In paper I, the statistical analysis was performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC). Statistical analysis for paper II-IV was performed with STATA version 16.0 and 18.0 (Stata Corp, College Station, Texas, USA).

4. Main results

Paper I – Estimated lifetime risk of venous thromboembolism in men and women

The incidence of VTE risk varies by sex and age. Some studies have reported an overall higher risk of VTE in men, especially when the VTEs triggered by female reproductive factors are excluded. However, higher mortality rates in men may have led to overestimation of lifetime VTE risk in men compared with women.

In a large cohort including the entire population of Denmark (>5 mill persons) in 1995-2016, we estimated the lifetime risk of VTE in men and women, taking into account competing risk by death. All first-time VTEs occurring in 1995–2016 were identified from the Danish National Patient Registry covering all Danish hospitals. The cumulative incidences of VTE were estimated in men and women with age as time scale, while accounting for the competing risk of death. Estimated lifetime risk was defined as cumulative incidence at age 100. In a simulation study, we excluded the proportion of female cases that could be attributed to reproductive risk factors and re-estimated the cumulative incidence.

We identified 123,543 incident VTEs. The cumulative incidence of VTE was 1.9% in women and 1.3% in men at age 50, 4.3% in women and 4.4% in men at age 70, and 9.3% in women and 8.1% in men at age 100 when competing risk by death was taken into account. After accounting for VTEs attributed to reproductive factors, the corresponding incidences in women were 1.2% at age 50, 3.2% at age 70, and 8.2% at age 100.

In conclusion, the estimated lifetime risk of VTE was slightly higher in women than in men when accounting for competing risk of death. Additionally, our simulation study suggested that reproductive risk factors contribute modestly to the estimated lifetime VTE risk in women.

Paper II – The Risk of Venous Thromboembolism Attributed to Established Prothrombotic Genotypes

The proportion of VTE events that can be attributed to established prothrombotic genotypes has been scarcely investigated in the general population. We aimed to estimate the proportion of VTEs in the population that could be attributed to established prothrombotic genotypes using a population-based case-cohort.

Cases with incident VTE (n=1,493) and a randomly sampled subcohort (n=13,069) were derived from the Tromsø Study (1994–2012) and the HUNT study (1995–2008). DNA samples were genotyped for 17 single SNPs associated with VTE. HRs with 95% CIs were estimated in Cox regression models. PAFs with 95% bias-corrected CIs (based on 10,000 bootstrap samples) were estimated using a cumulative model where SNPs significantly associated with VTE were added one by one in ranked order of the individual PAFs. Six SNPs were significantly associated with VTE (rs1799963 [Prothrombin], rs2066865 [FGG], rs6025 [FV Leiden], rs2289252 [F11], rs2036914 [F11], and rs8176719 [ABO]).

The cumulative PAF for the six-SNP-model was 45.3% (95% CI: 19.7–71.6) for total VTE and 61.7% (95% CI: 19.6–89.3) for unprovoked VTE. The PAF for prothrombotic genotypes was higher for deep vein thrombosis (DVT; 52.9%) than for PE (33.8%), and higher for those aged <70 years (66.1%) than for those aged 70 years (24.9%).

In conclusion, our findings suggest that 45 to 62% of all VTE events in the population can be attributed to known prothrombotic genotypes. The PAF of established prothrombotic genotypes was higher in DVT than in PE, and higher in the young than in the elderly.

Paper III – Proportion of venous thromboembolism attributed to recognized prothrombotic genotypes in men and women

VTE has a strong hereditary component, and studies have indicated an overall VTE heritability of up to 60%. Whether the individual and cumulative impact of prothrombotic genotypes on VTE risk is similar in men and women has not been addressed. Furthermore, whether known prothrombotic genotypes contribute to age-specific variations in risk of VTE in men versus women is not known. Therefore, we aimed to identify the individual and cumulative effect of common prothrombotic genotypes on VTE risk in men and women using PAFs. Additionally, we investigated the cumulative PAF in young, middle-aged and elderly men and women. The Tromsø Study (1994-2012) and HUNT Study (1995-2008) cohorts were used to create a case-control population consisting of 1,493 cases with incident VTE and a randomly sampled subcohort of 13,069 individuals. DNA samples were genotyped for 17 SNPs already associated with VTE. Individual PAF estimates with 95% bias-corrected CIs based on 10,000 bootstrap samples were estimated for SNPs significantly associated with VTE. In addition, a cumulative, 6-SNP model was constructed for men and women.

In women, the SNPs included in the cumulative model had individual PAFs of 16.9% for ABO, 17.6% for F11 (rs2036914), 15.1% for F11 (rs2289252), 8.7% for FVL, 6.0% for FGG, and 0.2% for F2. This resulted in a cumulative PAF of 38% in women. In men, the SNPs included in the cumulative model had individual PAFs of 21.3% for ABO, 12.2% for F11 (rs2036914), 10.4% for F11 (rs2289252), 7.5% for FVL, 7.8% for FGG, and 1.1% for F2. The cumulative PAF in men was 52%. For the age-specific analysis, the cumulative PAF varied in both sexes and was particularly pronounced in middle-aged (50-74 years) men (73%) compared to women (54.5%).

To conclude, our results indicate that the known prothrombotic genotypes that we have investigated contribute to a higher proportion of the VTE events in men than in women. The differential effect of prothrombotic genotypes on PAF in men versus women was especially pronounced in the middle-aged.

Paper IV – Body height and risk of venous thromboembolism in men and women

Several studies have shown an association between increasing body height and risk of VTE. However, while there is a clear association between body height and VTE risk in men, the findings have been somewhat inconsistent in women. Furthermore, it has been proposed that differences in VTE risk in men versus women could be attributed to differences in body height, presumably because men tend to reach a taller stature. However, this has only been investigated in one previous study, which only included middle-aged individuals at baseline.

In this merged cohort study consisting of 114,567 participants from the Tromsø Study (1994-2020) and the Nord-Trøndelag Health study (1995-2019), we used Cox regression to estimate the risk of VTE per 10 cm increase body height in men and women. In addition, we estimated whether the VTE risk in men versus women was affected after adjustment for body height in the young (19-49 years), middle-aged (50-74 years) and elderly (≥75 years).

We found that taller stature per 10 cm was associated with increased VTE risk in both men (HR: 1.34, CI: 1.25-1.44) and women (HR: 1.23, CI: 1.13-1.33). In the young (HR: 0.87, CI 0.70-1.08) and elderly (HR: 1.08, CI: 0.97-1.20) there was no difference in VTE risk in men versus women before adjustment, while the risk was higher in women after height adjustment (HR: 0.60, CI: 0.44-0.83 and HR: 0.83, CI: 0.71-0.97, respectively). In the middle-aged group, the risk of VTE was higher in men than in women (HR: 1.45, CI: 1.32-1.60), but diminished after adjustment for height (HR 0.98: CI 0.85-1.13).

In conclusion, we found that the risk of VTE in men versus women was considerably influenced by adjustment for body height at all ages. We also confirmed that taller stature was a risk factor for VTE in both men and women.

5. General discussion

5.1 Methodological considerations

5.1.1 Study design

In this thesis, we aimed to assess sex differences in risk of VTE in men and women. Risk is the probability of a future VTE, and we explored this challenge by exploring the following three areas: (i) the lifetime risk of VTE in men and women after accounting for competing risk by death, (ii) the association between prothrombotic genotypes and risk of VTE in the general population, and specifically in men and women, (iii) the influence of body height on risk of VTE in men and women. All four papers presented in this thesis were epidemiological studies. Three of the studies had prospective designs derived from population-based cohorts, while one study had a prospective design created by merging national, population-based registries.

In paper I, we merged multiple Danish, population-based registries to create a nationwide cohort population in order to estimate the lifetime risk of VTE in men and women. A population-based registry aims to incorporate all individuals with a certain attribute, event or exposure in a geographic area within a defined period of time (147). An advantage with population-based registries is prospective data accumulation over long time periods, and ideally, the recording of an exposure before the outcome occurs (148). Population-based registry studies are therefore efficient in terms of both time and costs and makes it possible to study the incidence of disease on a national level (148). Additionally, they allow for a large study size, comprehensive population coverage and less probability of differential misclassification. Nonetheless, registry-based studies often lack clinical information making it challenging to assess the severity and progression of disease. Furthermore, since registry information is collected with a defined purpose rather than answering a specific research question, registries may be incomplete and information on some variables may be missing (149). However, this is not likely to affect our findings, since the thesis focuses on incident VTE, rather than disease severity or recurrence. Furthermore, the national health registries in the Nordic countries have a strong reputation internationally due to their tax-supported, universal health care coverage, and mandatory documentation of all health services. In addition, the unique personal number allows linkage between several national registries like birth, death, hospital discharge, outpatient registries, and more (150).

Paper II-IV consisted of study populations derived from the prospective cohorts Tromsø and HUNT studies. The term cohort is derived from Latin, and originally referred to a 300-600-man unit in the Roman army. In medicine, a cohort design follows a defined study population until either the outcome of interest (for instance VTE), a censoring event (e.g. death) or end of the follow-up period (151). In prospective cohort studies, such as the Tromsø and HUNT studies, exposure (i.e., body height) is recorded at study entry, and the occurrence of the outcome is registered when it occurs, or the individual is censored at end of follow-up. A major benefit of cohort studies is the possibilities to obtain a large population size and multiple outcomes that may be associated with multiple exposures. Other important strengths of the cohort design are the possibility to estimate both incidence and relative risks and several outcomes at the same time, in addition to a clear temporal sequence between exposure and outcome, which minimizes the risk of recall bias (152). However, cohort studies have some considerable drawbacks. The main challenges are the considerable economic and time-consuming demands, and cohort studies have limited usefulness when investigating rare or latent outcomes. In addition, cohort studies are vulnerable to differential loss to follow-up, which will be discussed as a potential bias further down. Further, long follow-up time from classification to event/censoring increases the chance of a change in exposure status, which could impact the validity of the findings (150). For instance, a single measurement made several decades before an event takes place regarding an individual's smoking status, blood pressure or weight is not necessarily representative of the person's exposure status at the time of the event. In our cohorts, our main exposure variables in papers II-IV are body height and genetics, which are not susceptible to large variations over time in an individual. Therefore, even single measurements are sufficient to capture an individual's exposure status for such exposures.

In papers II and III, a case-cohort design was utilized. As implied by its name, the study design implements features of both case-control and cohort studies. In a case-cohort, every person that experiences the outcome of interest during the follow-up period in the source cohort is included as a case. Additionally, every person in the cohort has an identical likelihood of being included in the study as part of a subcohort, regardless of whether the individual

experiences the outcome of interest or not (figure 8) (150). This creates an overlap between the cases and the subcohort population. The overlap, and the creation of the subcohort at baseline permits time-to-event analysis. By design, case-cohorts are an efficient and cost-effective way of obtaining additional information from the cohort that was not obtained or measured for the whole cohort (153).

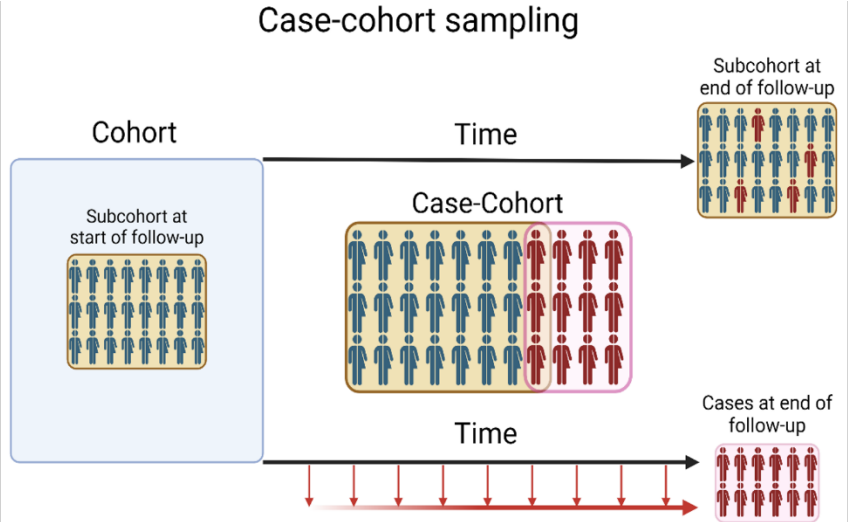


Figure 8. *Case-cohort-sampling. Subcohort members represented by a yellow box are selected from the baseline cohort. Cases from the cohort are selected every time they occur and are represented by red arrows. The case-cohort has some overlap, since VTE events also occur in the subcohort. This is represented by the merged boxes (108).*

5.1.2 Validity

Validity in epidemiological studies is broadly divided into ***internal and external validity.*** Internal validity addresses whether an observed association is true for the population under study, while external validity deals with whether an observation from the study can be generalized to other populations than the population under study (150). One of the main benefits of population-based cohort studies and population register studies is that they are recruited from the general population (141). Therefore, the internal validity is intact, unless there are errors in the recruitment, data gathering or analytic process (for instance, confounders that are not accounted for). Bias in the recruitment and/or follow-up has the potential to limit the internal validity and generalizability of population-based cohorts. To

counteract this, high participation rates and minimal loss during follow-up are important components to ensure strong external validity (154, 155).

5.1.3 Bias

Bias, or systematic errors, are an element in all epidemiological studies, and mostly affect the internal validity of the study. A systematic error differs from a random error in that it's effect will be present regardless of sample size, unlike random errors, whose effects will be reduced by an increase in sample size (152). Three general categories of challenges to internal validity are ***confounding***, ***selection bias*** and ***information bias***. They can occur in the design, execution or analysis of the study and lead to mistaken estimates of an exposure's influence on disease risk.

Information bias is a methodological error that occurs because the information collected about study subjects is erroneous. Further, such errors lead to inaccurate information about exposures or outcome (152). In other words, the information is ***misclassified***. Misclassifications can either be ***differential*** or ***nondifferential***. Differential misclassifications are systematic errors that are related to the occurrence of the disease (i.e. VTE), while nondifferential misclassifications are not related to the disease. Measurements of exposure variables in prospective cohort studies are typically conducted before the outcome occurs. Therefore, the most typical type of misclassifications in cohort studies are nondifferential misclassifications. In this thesis, such a misclassification could occur during body height measurement. All study subjects were measured before the occurrence of the outcome, and therefore, any measurement errors would be random. Hence, any misclassification would be equally distributed between those who contract the disease, and those who do not contract the disease. An example of a differential misclassification is a faulty blood pressure apparatus that is only used to measure the blood pressure of the cases, therefore leading to a misclassification of the exposure in all cases (152).

Differential misclassification could occur for both exposure and outcome. In the Tromsø and HUNT study, relevant exposures like BMI, body height and blood sampling for genotyping

was procured by trained personell, and at baseline. Therefore, there is little risk of a differential misclassifation concerning the relevant exposures. In both Norway and Denmark, all in- and outpatient hospital diagnoses are registered in national registries. Moreover, diagnoses of VTE are not made by a general practitioner without referral to a hospital, therefore, the VTE registries likely capture most of the VTE events. In addition, both the Tromsø and HUNT studies have objectively confirmed VTE diagnoses through radiological procedures and review of medical documents by trained personnel (27, 72). Denmark's registry, the DNPR, is one of the world's oldest nationwide hospital registries, and individual-level linkage with other nationwide registries is secured through the CRS. Furthermore, the CRS includes comprehensive information on birth dates, deaths and migration, further securing objective measures for the follow-up period (149). The DNPR has collected data from all Danish hospitals with complete nationwide coverage from 1978 until today. Since 1995, the DNPR has included information on all somatic outpatients (141). The positive predictive value (PPV) for DNPR varies significantly by disease, but VTE diagnoses in Denmark are usually made by trained specialists, and a validation study of DNPR data reported PPV of 86% and 90% for diagnoses of first-time DVT and PE (156). Therefore, the risk of misclassification of outcome does not appear to be a major problem in this registry.

Selection bias is an error that arises from the selection process, and from factors that influence study participation. It occurs when the association between exposure and disease differs for those who participate in the study, and those who do not participate in the study. Therefore, the study participants are not representative of the target population. Cohort studies like the Tromsø and HUNT studies are vulnerable to selection bias through ***self-selection*** since subjects who voluntarily take part in cohort studies generally are healthier than those who do not participate (157). This challenge is largely countered by the high attendance rates of the Tromsø and HUNT studies. Further, earlier studies have indicated that even estimates from population-based cohort studies with attendance rates of 30%, only differs marginally from estimates in population-based cohorts with attendance rates of up to 70% (158). Additionally, the Tromsø and HUNT study has experienced a slight decrease in participation rates in the last decades, which has been the global trend in large, epidemiological studies since the 1970s (159). In the Tromsø study, there has been a moderate reduction since Tromsø 4, but the attendance rate was stable between 6 and 7 (Tromsø 4: 77%,

Tromsø 5:79%, Tromsø 6: 66%, Tromsø 7: 65%) (137). For the HUNT study, there has been a larger reduction in attendance rate, but the study has also stabilized its attendance rate (HUNT2: 70%, HUNT3: 54%, HUNT4: 54%) (160). Nevertheless, the possibility of bias is always present, and in both Tromsø and the HUNT study, the participation rates are particularly low among young, single males and individuals aged ≥80 years (137, 160). An additional form of selection bias that will be addressed later in the thesis is ***the competing risk of death***.

In the DNPR, the risk of selection bias is minimal due to the universal health care system with virtually complete follow-up of all patients owing to the Danish CRS (141). In two of our studies, genetic material from blood samples were used. Potentially, a self-selection bias could occur if individuals with known genetic conditions were less willing to participate in our cohort study than individuals with no known genetic conditions. However, this does not seem likely since both allele frequencies and effect estimates in the studies are comparable to other, international studies on genetic variation (161). Additionally, existing literature has not found a clear selection bias in other cohorts (162, 163). Conversely, a Norwegian study on adolescents found that male sex, poor self-reported health and low socio-economic status were predictors for not consenting to provide DNA samples (164).

5.1.4 Confounding

Confounding refers to situations where non-causal associations are observed between a given exposure and outcome, because of the influence of another variable, commonly labeled as a confounder. In short, confounding leads to a confusion of effects, and threatens the internal validity of the study. A confounder must fulfill three conditions: (i) It must be associated with the exposure and the outcome, (ii) it must be unevenly distributed between the study groups, and (iii) it cannot be part of the causal

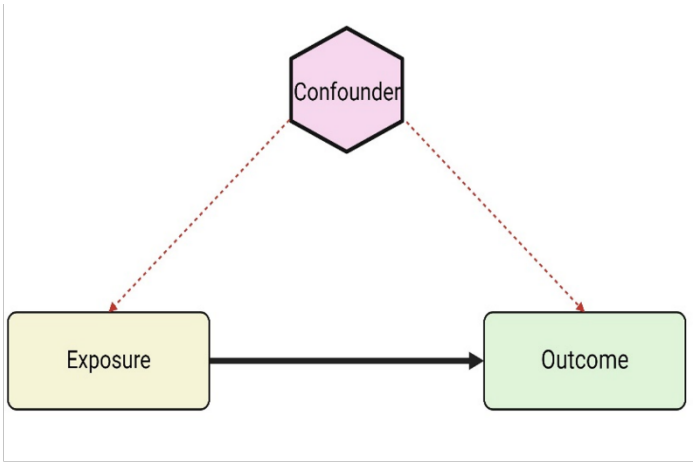


Figure 9. *Confounding (152).*

pathway from exposure to outcome (figure 9) (152). A classic example of a confounding factor is the prevalence of birth defects by birth order. There is a larger risk of birth defects among women who give birth to their fifth child, compared to women who give birth to their first child. However, birth order and age of the mother is highly correlated. Therefore, the association between birth order and birth defects is confounded. There are several ways to account for confounding, either during the design of the study through for example matching or during the statistical analysis by adjustment, stratification or standardization, but only if information on potential confounding factors is available. If not, the results could be subject to residual confounding, where not all relevant confounding factors are accounted for.

In this thesis, we stratified by sex in papers I, III and IV. Additionally, papers III and IV included age-stratification into the young (20-49 years), middle-aged (50-74 years) and elderly (≥75 years), while paper II stratified on those over and under 70 years of age. The main benefit of stratification is the formation of subgroups that have more in common with each other than the rest of the population (150). For an illness like VTE, where the relative risk varies substantially among the sexes throughout the lifespan, there are considerable benefits to comparing age ranges in order to ensure that we lose as little information as possible on the association between body height and prothrombotic genotypes, and VTE in men and women.

Regression methods were used in all the papers included in this thesis, and it was also used to account for the confounding factor of age. As the risk of VTE increases with age at an exponential rate, and the underlying baseline risk in a 25-year-old is much lower than in a 75-year-old, it is essential to account for when investigating associations between exposures and VTE. Also, age is an especially important factor to account for in the study on body height since physical stature declines with age (165). Considering that VTE risk increases significantly with age, not accounting for the effect of age could potentially lead to a significant underestimation of taller stature's association with VTE risk. In regression analysis, age can be accounted for in many ways, but in a prospective study, an effective way is to use age as the time scale. This

contrasts with using calendar time as time scale, where length of time under follow-up is used instead (figure 10) (166).

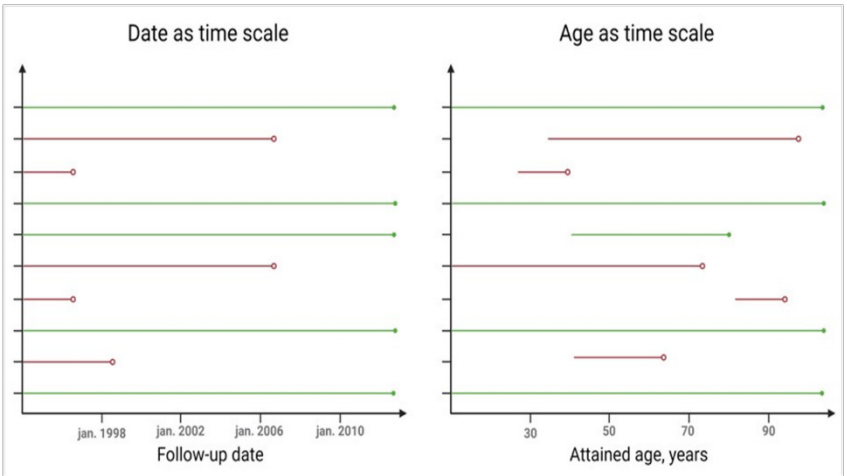


Figure 10. *Date and age as time scale illustrated (166).*

Another effect related to age that could affect the association between body height and VTE in men and women is potential birth cohort effects. Birth cohort effects are variations over time, for one or more characteristics among individuals defined by some shared experience such as year or decade of birth (167). For instance, those raised during the war or during the ensuing years with extensive rationing could be more susceptible to disease or shorter in stature due to lack of nutrients. When considering whether birth cohort effects could affect the association between body height and VTE in men versus women, the main question is whether there are any differences in body height time trends in men and women. Multiple studies have shown that the average body height in European countries is increasing, and this is also true in our population. A recent time trend study in the Tromsø study population, found that the sex-specific average body height increased by 3.4 cm in men and women from the 1930-1939 birth cohort to the 1970-77 birth cohort (168). Similar results have previously been published in HUNT (169). Therefore, one way of accounting for potential birth cohort effects is by conducting what is known as a sensitivity analysis, where separate analyses are run for different birth cohorts. For instance, estimation of the association between body height and VTE in men and women, could be conducted separately in those born in 1930-1950 from those born in 1950-1970. However, since the differences in body height in men and women seem to be consistent over long time periods, the potential effect most likely would lead to an underestimation of the association between body height and VTE risk. Therefore, birth cohort effects would have little to no impact on comparisons on the association between body height and VTE if age effects have been accounted for. However, birth cohort effects could potentially have a differential impact on VTE identification. In the 1990s, there was

considerable development in the diagnostic tools of VTE, and especially in the use of more sensitive tools like CTPA in addition to more clinical awareness about VTE. Potentially, this could have led to more incident VTEs in either men or women if the new diagnostic methods or increased diagnostic awareness were more sensitive for one of the sexes. In paper I, where we investigated the overall lifetime risk, we conducted a sensitivity analysis to see whether there were marked differences in the number of VTE events in men and women in the time periods 1995-2005 and 2006-2016, and we found no difference.

5.1.5 Competing risk of death

Censoring is a fundamental element in survival analysis, and the concept of non-informative censoring is an important assumption in traditional survival analysis. If an individual is lost to follow-up to for example migration, that individual is treated as censored because whether that person experienced the outcome of interest or not, is unknown. In short, we are uninformed about the subject's status after the censoring date.

A competing risk event is an event (e.g. death) whose occurrence prevents the occurrence of the event of interest (e.g. VTE). A competing event prevents the observation of an event of interest or alters the chance that this event might happen. The incidence of VTE increases significantly with age, and the competing risk therefore also increases significantly throughout a person's life. The difference in censoring happens when a competing risk occurs. In traditional Kaplan-Meier (KM) method, the competing event is treated the same as any other reason for censoring. This leads to an overestimation of risk at the next event of interest. Using the CIF, the competing risk is treated as a failure. The differences in how the methods affect cumulative incidence is illustrated in figure 11.

Follow-up time (days)	Status	Kaplan–Meier method		Competing risk method using CIF	
		KM	1-KM(t)	S(t)	CI(t)
0	–	1	0	1	0
7	Ev	1 × 9/10 = 0.9	0 + (1 × 1/10) = 0.1	1 × 9/10 = 0.9	0 + (1 × 1/10) = 0.1
11	Cen	0.9 × 9/9 = 0.9	0.1 + (0.9 × 0/9) = 0.1	0.9 × 9/9 = 0.9	0.1 + (0.90 × 0/9) = 0.1
15	CR	**0.9 × 8/8 = 0.9**	0.1 + (0.9 × 0/8) = 0.1	**0.9 × 7/8 = 0.79**	0.1 + (0.90 × 0/8) = 0.1
18	Ev	0.9 × 6/7 = 0.77	0.1 + (0.9 × 1/7) = 0.23	0.79 × 6/7 = 0.68	0.1 + (0.79 × 1/7) = 0.21
23	Cen	0.77 × 6/6 = 0.77	0.1 + (0.9 × 0/6) = 0.23	0.68 × 6/6 = 0.68	0.21 + (0.68 × 0/6) = 0.21
27	CR	**0.77 × 5/5 = 0.77**	0.1 + (0.9 × 0/5) = 0.23	**0.68 × 4/5 = 0.63**	0.21 + (0.68 × 0/5) = 0.21
31	CR	0.77 × 4/4 = 0.77	0.1 + (0.9 × 0/4) = 0.23	0.63 × 3/4 = 0.42	0.21 + (0.63 × 0/4) = 0.21
33	Ev	0.77 × 2/3 = 0.51	0.23 + (0.77 × 1/3) = 0.49	0.42 × 2/3 = 0.28	0.21 + (0.42 × 1/3) = 0.35
35	Ev	0.51 × 1/2 = 0.26	0.49 + (0.51 × 1/2) = 0.74	0.28 × 1/2 = 0.14	0.35 + (0.28 × 1/2) = 0.49
36	Cen	0.26 × 1/1 = 0.26	0.74 + (0.26 × 0/1) = 0.74	0.14 × 0/1 = 0.14	0.49 + (0.14 × 0/1) = 0.49

CR= Competing risk, Ev= Event of interest, KM=Kaplan-Meier, CIF=Competing incidence Function, S=survival, CI=cumulative incidence, Cen=Censored

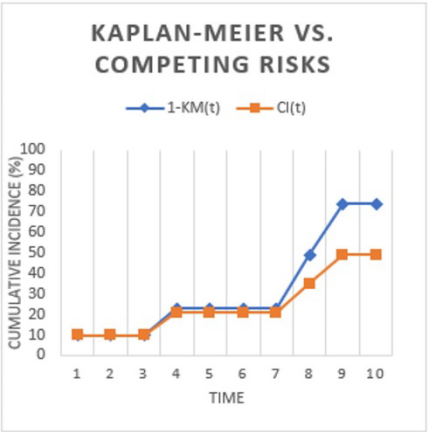


Figure 11. *Example of how the competing risk of death influences the cumulative incidence of the event of interest.*

5.1.6 Population attributable fraction (PAF)

In papers I, II and III, we used PAF (figure 12) to quantify the proportion of VTEs that could be attributed to known reproductive (paper I) and prothrombotic risk factors (papers II and III). The PAF estimate is dependent on the increased risk associated with the exposure, and the prevalence of the exposure (170). PAF values are usually larger than other comparable genetic measures, like heritability (171) which quantifies the effects on the variability of risk at the population level. Although PAF and heritability measure different aspects of genetic contributions to disease risk, the two measurements are related (172). While PAF is a useful tool to analyze the influence of genetic factors, it can be overestimated when the risk factor prevalence is very high, due to its direct dependence on prevalence (171, 173). The complete, cumulative PAF models used in our study had a high prevalence, and consequently the percentages might be somewhat overestimated. However, since the prevalence of the SNPs was similar in men and women, our PAF estimates would still allow for comparison between the sexes. Importantly, there is a difference between the attributable fraction of events among those exposed to a certain risk factor, and the population attributable fraction. For instance, individuals with an antithrombin deficiency have a high risk of VTE compared to those not exposed to antithrombin deficiency. but overall, AT deficiency is rare, and accounts for only a small proportion of all VTE events (150).

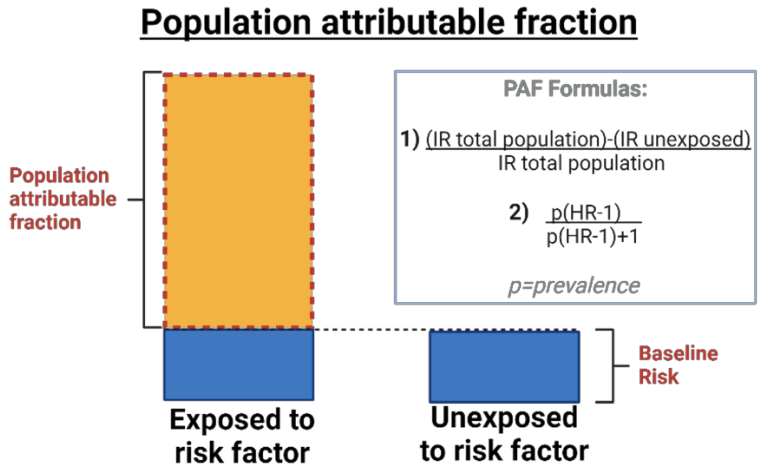


Figure 12. *Population attributable fraction illustrated.*

There are several ways to calculate the PAF. In this thesis, two different PAF formulas have been applied. In paper I, the formula used was based on IRs: $\frac{IR_{total\ population} - IR_{unexposed\ population}}{IR_{total\ population}}$, which was used to estimate the proportion of VTE events in women aged 15-49 years that could be attributed to reproductive risk factors in the Danish population. In paper II and III, the formula $\frac{p(HR-1)}{HR+1}$ was employed to analyze the proportion of events attributable to known prothrombotic genotypes (174).

5.2 Discussion of main results

5.2.1 Lifetime risk of venous thromboembolism in men and women

In paper I, we used the complete population of Denmark from 1995 to 2016 to investigate the age-specific cumulative incidence and estimated lifetime risk of VTE in men and women when accounting for the competing risk of death. We found that the estimated lifetime risk of VTE was 9.3% in women and 8.1% in men, which indicates that women have a slightly higher risk of VTE than men. The competing risk of death clearly impacted the cumulative risk estimates of VTE in both sexes, but especially in men, due to the increased mortality rate in men compared to women at all ages.

Several studies have investigated the sex-specific risk of VTE (25, 26, 29, 55, 107, 110, 111, 119, 175, 176), but the results have varied considerably between studies. The varying results could be due to differences in study designs, age range of the population under study, or the statistical methods that have been used. To determine whether differences in results between studies could be explained by differences in the age range of the study populations, we decided to explore the sex-specific risk of VTE in a nationwide cohort that consisted of individuals in the entire age range, and assess the incidence rates according to different age-groups, as well as the cumulative incidence according to increasing age. The main advantages of using the complete population of Denmark in 1995 as our source cohort were fourfold: (i) It ensured that incidence rates in all age groups were captured, (ii) the DNPR is expected to have a near-complete recording of all diagnosed first time-VTE events in Denmark in the study period since VTE diagnoses are mostly made by specialists, (iii) the registry-based nationwide approach ensured negligible loss to follow-up since linkage through the CRS provided us with complete information on date of emigration and death.

The age-specific incidence rate patterns in our population corresponded well with those reported in previous studies. Among individuals aged 20-49 years, we found an IRR of 1.4 for VTE in women compared to men. A higher incidence rate among women in this age range is consistent with results from the HUNT study (IRR: 1.6) (27), HLU study (IRR: 1.6) (110) and REP study (IRR: 1.6) (29). Among middle-aged individuals, women had a lower IR of VTE than men, which corresponded to an IRR of 0.8 for women versus men. The same pattern was found in the HUNT study (IRR: 0.8), Tromsø Study (IRR: 0.8 in individuals aged 50-70), REP

study (IRR: 0.7) and HLU study (IRR: 0.7) (25, 27, 29, 110). In the elderly, the IR of VTE in men and women in our cohort was essentially similar, resulting in an IRR of 1.0. These results corresponded well with the results from the HUNT study (IRR: 1.0), the Tromsø Study (IRR: 1.0) and the HLU study (IRR: 1.2) (25, 27, 110). In contrast to our findings, the REP study found a higher incidence in men (IRR for women versus men: 0.8), and the LITE study reported a twofold higher incidence in men compared to women aged ≥75 years (29, 107).

When analyzing the entire lifespan, the overall IR of VTE in our study was 1.28 per 1000 person-years in women and 1.17 per 1000 person-years in men, which yielded an overall IRR of 1.1. In agreement with our findings, the HUNT study (participants aged >20 years) and the Tromsø study (participants aged ≥25 years) reported an IRR of VTE of 1.0 for men versus women (25, 27), while the REP study (participants of all ages) and the HLU study (participants aged ≥15 years) reported an IRR of 1.1 for women compared to men (29, 110). However, the REP study also reported an age-adjusted IRR of 0.8 in women compared to men (29). In addition, the DCH study (participants aged 50-64, IRR: 0.6), and the LITE study (participants aged ≥45 years, IRR: 0.7) also reported higher incidence rates in men (55, 177). All the studies that reported higher overall incidence rates in men were composed of middle-aged to elderly individuals at baseline, which corresponds well to our findings in the same age groups. Therefore, despite some minor differences, the age-specific incidence rates of VTE in men and women in our study followed the same pattern variations across age groups as most of the previously published studies. This further supports that while the overall sex-specific incidence of VTE in men and women reported in previous studies varied somewhat, these variations can likely be explained by the age distribution of the population under study.

Since the IRs of VTE in men and women vary across different age groups, the cumulative lifetime incidence of VTE in men and women is of interest. Furthermore, since both the risk of VTE and death increases exponentially with age (144), and high death rates are known to lead to an overestimation of cumulative incidence measures (178), it is important to account for death as a competing event when assessing life-time risk. Additionally, VTE risk estimates in men could be especially affected since men have a higher death rate than women at all ages (117). The only publication we know of that has previously estimated the lifetime risk of VTE in men and women and accounted for the competing risk of death consisted of two American

cohort studies, the CHS and the ARIC study, which comprised of participants aged 45-64 years and ≥65 years, respectively (119). The participants were followed to a maximum age of 85, and the lifetime risk of VTE was 8.4% in women and 7.7% in men, which corresponded well with our findings of 9.3% in women and 8.1% in men. The slightly higher estimate found in our study is most likely due to the inclusion of individuals aged 0-100 years, which enabled us to look at the whole lifespan.

Another point of contention regarding VTE risk in men and women is the contribution of reproductive risk factors in younger (<50 years) women. Young women have a swift rise in the cumulative incidence of VTE compared to young men, which is mostly caused by pregnancy and estrogen-containing oral contraceptives (45, 88). In our study, young women had a higher risk than young men. However, if we consider the overall risk of experiencing a VTE throughout the entire lifespan, the risk of VTE among the young was relatively low in both men and women compared to the risk of experiencing a VTE at a later point in life. In fact, we found that merely 22% of all VTE events in women and 19% of all VTE events in men occurred before age 50. Hence, while the relative risk difference in men and women among the young is considerable, the absolute risk is low in both sexes compared to the risk in older age groups (27).

In 2016, a study based on the MEGA case-control population, which consisted of adults aged 18-70 years, reported that the risk of a first-time VTE was twice as high in men compared to women after exclusion of women with reproductive risk factors (120). However, the study included few females without reproductive risk factors, was based on relative measures, the cases had survived initial treatment with anticoagulation and the upper age limit at inclusion was 70 years. In our study, we found that half of all VTEs in the female population occurred after the age of 70, a stage of life where women are not exposed to reproductive risk factors. Therefore, we wanted to address the effect of reproductive risk factors on the lifetime risk of VTE and investigate whether men had a twofold higher risk of VTE compared to women in a lifetime perspective when reproductive risk factors were accounted for. Unfortunately, we did not have exact information on pregnancy and the use of oral contraceptives in our dataset. Hence, we conducted a simulation study where 45% of all VTE events in females aged 15-49 were treated as if they had not occurred. The proportion of VTE events attributed to oral contraceptives was arrived at using IRs provided by a nationwide Danish study on hormonal

contraception and risk of VTE (93). There, the IR of VTE in all women aged 15-49 was reported to be 4.03/10,000 woman-years, while the IR among former or never users of oral contraceptives was 3.01/10,000 woman-years. This translated to a PAF of 25% for oral contraceptives. In another nationwide Danish study on pregnancy-related VTE, the risk of VTE in non-pregnant women was 3.6/10,000 woman-years (100). This corresponded to a PAF of 10%. To ensure that we did not underestimate the proportion of events attributable to reproductive factors, we chose to treat 45% of all VTE events in females aged 15-49 years as if they had not occurred. We concluded that while the lifetime risk in women was somewhat reduced when reproductive factors were accounted for, the lifetime risk was still 8.2% in women, and thereby very similar to the lifetime risk in of 8.1% in men. Considering that the lifetime risk in women dropped with only 1.1% when we ignored 45% of VTE events in women aged 15-49 years, it is likely that the lifetime risk of VTE in women would be reduced with approximately 2.2-2.3% if we had ignored all VTE events among women in this age group. Thus, if we had assumed that all VTE events in women at reproductive age could be attributed to reproductive risk factors, the lifetime risk of VTE in women would still be around 7%. Furthermore, it is highly unlikely that all women who experience a VTE due to reproductive factors would go through life without experiencing a VTE due to other circumstances. Therefore, we most likely overestimated the effect of reproductive risk factors, and our findings indicate that the lifetime risk of VTE is essentially similar in men and women when accounting for reproductive factors.

Several studies have reported a higher risk of recurrent VTE in men compared to women, and this could suggest a higher inherent risk of first-time VTE in men when accounting for reproductive factors (112, 179). In 2011, Douketis et al. reported that the risk of a recurrent VTE was 2.2-fold higher in men compared to women after a first unprovoked VTE, and that it remained 1.8-fold higher after adjustment for hormone-associated VTE, while no sex-difference was found among individuals with a provoked event (179). However, the mean length of follow-up of the included individuals was only 27 months, and considering that approximately 30% of the included female VTE cases in the review were hormone-associated, and they were significantly younger than the rest of the included individuals (mean age 40 years vs. 58 years), such a short follow-up time could affect the estimates. In a systematic review and meta-analysis on recurrent VTE from 2019 the cumulative risk difference was

merely 1.4-fold higher in men than in women, thereby indicating that the difference in recurrence risk is not as large as previously thought (112). However, the follow-up time was quite short in this study as well, with only a handful of studies exceeding two years of follow-up. Additionally, the meta-analysis did not assess recurrence risk stratified by age groups, which could have revealed an age-sex interaction, did not adjust for potential confounders, such as BMI and body height, and did not take the competing risk of death into account (which would be important as men have a higher death rate).

Whether the presenting location of first-time VTE events differ in men and women has previously been discussed. In a case-control study based on the MEGA, RIETE and Hokusai-VTE studies, Scheres et al. found that a higher proportion of women presented with PE than men, with the difference ranging from 3.1% to 8.5% (83). However, these were relative proportions, and not absolute risks, which would be required to clearly demonstrate potential sex differences in the presenting location of VTE. In our study, we found a 2-percentage-point higher proportion of first time PE-events among women compared to men (41.9% vs. 39.1%). Nonetheless, the estimated lifetime risk measurements did not reveal any considerable differences in anatomical locations of DVT (5.4% vs. 4.9%) or PE (4.0% vs. 3.4%), which is consistent with other studies that have not found any substantial differences in the presenting location of DVT and PE in women compared to men (25, 26, 107). Thus, we did not find any indication that the presenting location of VTE vary considerably in men and women.

The main aim of this paper was to estimate the lifetime risk of VTE in men and women, and ideally, the best way to estimate this would be to follow a cohort throughout an entire lifetime. However, since the DNPR does not have complete information on in- and outpatients from before 1995, we were not able to follow our cohort from cradle to grave. Nonetheless, the long follow-up time of 20 years in a complete, nationwide cohort that included individuals of all ages likely yields a robust indication of the lifetime risk in men and women. Furthermore, even if we had information on all VTE events from 1900 until today and could estimate the real lifetime risk in this period, this would increase the likelihood of bias due to time trends and birth cohort effects and could weaken the generalizability of our results to current populations (167). We tried to account for birth cohort effects and time trends by conducting a sensitivity analysis where we divided the study period into 1995-2005 and 2006-2016, and calculated the

cumulative incidence of VTE in men and women in each period while accounting for the competing risk of death. The results displayed that the incidence of VTE had increased in both sexes, but the incidence patterns were stable in men and women, and therefore there were no obvious sex-differences due to birth cohort effects. Additionally, a Danish study on temporal trends from 2006 to 2015 further supports this finding (16). Hence, while we cannot rule out the potential presence of birth cohort effects that could differ in men and women, we have no indication that they have affected our results in any significant way.

5.2.2 Prothrombotic genotypes and VTE

In paper II, the proportion of first-time VTE events that could be attributed to known prothrombotic genotypes in a Norwegian population was estimated. To achieve this, we created a 6-SNP cumulative PAF model based on the highest individual PAF estimates in our population and found that 45% of the VTE events in our population could be attributed to these 6 SNPs. Furthermore, using the same cumulative model, we found that 62% of all unprovoked VTEs and 66% of all VTE events occurring before age 70 could be attributed to known prothrombotic genotypes.

The cumulative model was built with the intention of exploring the genetic contribution of multiple prothrombotic genotypes on the risk of VTE. First, we calculated hazard ratios and the individual PAFs, and based on these measures, we constructed a cumulative PAF model where we combined multiple SNPs. For each step, we added one SNP. The SNPs used were added in the following order: rs8176719 (ABO), rs2036914 (F11), rs2289252 (F11), rs6025 (FVL), rs2066865 (FGG) and rs1799963 (F2). In the model, we saw an increase in the PAF estimate up to and including the addition of the fifth SNP, where a peak estimate of 45.3% was reached. With the addition of the sixth SNP, F2, there was no further increase in the PAF, which indicated that the genetic contribution on the risk of VTE is explained by relatively few SNPs. The rationale for using a limited amount of SNPs to evaluate the PAF of prothrombotic genotypes is supported by a 5-SNP genetic risk score developed by De Haan et al., which found that 5 SNPs had the same predictive capabilities as a risk score consisting of 31 SNPs (129). Interestingly, all 5 of the De Haan-score-SNPs were found in our model (FVL, F2, ABO, FGG, rs2036914), which further supports that the included SNPs contribute to a large proportion of VTE events in the general population. Heit et al. also used three of the same SNPs (ABO, FVL, F2) in a joint model which yielded a PAF of 35% (126). Taken together, these findings suggest that much of the genetic risk of VTE in the total population can be attributed to a small number of SNPs. For unprovoked VTEs, we found that more than 60% of events could be attributed to known prothrombotic genotypes. While we are not aware of any previous PAF estimates of prothrombotic genotypes on unprovoked VTE, our finding is in agreement with studies reporting a higher prevalence of thrombophilia among individuals with unprovoked VTE (131, 180).

The individual PAF estimates of the SNPs included in the 6-SNP cumulative model were mostly in accordance with the previously published literature. We found that non-O-blood types contributed to the largest proportion of VTE events, with a PAF estimate of 19%, which is in keeping with a Swedish population-based cohort, which reported a PAF of 20% for non-O-blood types (142). The considerable proportion of events attributable to non-O was mainly explained by the relatively high prevalence of 62% and a modest VTE-risk increase of 38%. Accordingly, several case-control studies have found that non-O-blood type has the largest influence on VTE risk in the population (120, 126). Both F11 SNPs included in our model had sizable PAF estimates of 13-14%, but the PAF values were considerably lower than the PAF values of 28% and 24% previously reported in a combined case-control population (181). The associations between FVL and F2 and VTE risk on a population level have been firmly established previously (120, 126, 142, 180). Notably, the average age of participants in previous study populations where PAF has been estimated has usually been lower than in our cohort population (120, 126), and some studies recruited participants who were referred to thrombophilia clinics (126). Both the lower age and the recruitment of participants that were referred to thrombophilia clinics may have contributed to an increased prevalence of prothrombotic risk factors among the VTE cases included in these studies compared to our population, which consisted of unselected VTE cases from the general population. Additionally, differences in study design could also account for some of the observed differences, since the risk estimates (i.e., ORs) from case-control studies often are higher than those from cohort studies (150). Of note, our risk estimates for FVL, F11, FGG and ABO were similar to those reported in a genome-wide association study (GWAS) meta-analysis by Lindstrom et al. which pooled the results of 18 studies (60).

The PAF estimates in our study could be overestimated due to their dependence on prevalence. This is a particular challenge for our cumulative PAF models since the prevalence becomes quite high (96%). Furthermore, the rs8176719 used in this study is not optimal for evaluating VTE risk mediated by the ABO locus as it does not consider the A2 and O2 blood groups which are associated with a lower risk of VTE compared with A1 and B (182). However, as the prevalence of A2 and O2 in the population is low (haplotype frequencies <5% and <1%, respectively), this is likely to have a negligible effect on the PAF estimates.

Whether certain prothrombotic genotypes contribute differently to the formation of thrombi in specific anatomical locations is a topic of major interest, particularly due to the observed difference in thrombus location in FVL carriers which has been reported in several studies, and is known as the “FVL paradox” (130, 183, 184). According to the MEGA case-control study, FVL carriers have a threefold increased risk of experiencing a DVT than a PE (185). In our study, a larger proportion of DVT events than PE events were attributed to prothrombotic genotypes. The difference between presenting location was mainly explained by FVL and ABO. For FVL, the individual PAF estimates were 11.2% in DVT and 3.3% in PE, indicating that the fraction of DVT events attributed to FVL is more than 3 times higher than the proportion of PE events attributed to FVL. In ABO, the difference was more marginal, with 21.2% and 15.6% of DVT and PE events attributable to ABO, respectively. For FVL, it has been theorized that the difference could be explained by the formation of more stable clots that are less susceptible for embolization (184). Potentially, the same could hold true for ABO.

To assess the impact of individual and multiple prothrombotic genotypes in the young and elderly, we investigated the influence of prothrombotic genotypes on VTE risk in individuals older and younger than 70 years. We found that the prothrombotic genotypes contributed more to the occurrence of VTE among individuals <70 years. The higher PAF for prothrombotic genotypes in the younger age group was particularly explained by higher HRs of VTE for the SNPs rs8176719 (ABO), rs2303914 (F11), and rs2066865 (FGG). In accordance with our findings, earlier studies have reported an age effect for the association between family history and the risk of VTE, with the highest risk found in the younger age groups (186, 187). Additionally, among those aged 20 years or younger who had experienced a VTE event, nearly 50% had prothrombotic genotypes compared with only 22% among those who experienced their first event aged 70 years and older (131), suggesting that individuals with genetic risk factors experience VTE at a younger age. As aging is associated with an accumulation of acquired and environmental risk factors, the relative contribution of the genetic factors may be diluted with increasing age. The age effect may also be explained by the phenomenon “attrition of susceptibles” where those highly vulnerable have higher risk of developing a thrombus at a younger age than later in life.

Proportion of VTE events attributable to known prothrombotic genotypes in men and women

In Paper III, we investigated the individual risk of VTE according to 17 established prothrombotic genotypes in men and women. Additionally, we estimated the total and age-specific cumulative PAF by using the same 6-SNP-model established in paper II. We found that the allele frequencies of the included SNPs were similar in men and women, but the relative risk measures and individual proportion of VTE events that could be attributed to prothrombotic genotypes varied somewhat for the included SNPs, ABO, F11 rs2036914 and rs2289252, FVL, FGG and F2. For the 6-SNP-model, we found that the fraction of first-time VTE events that could be ascribed to prothrombotic genotypes differed between sexes and was 38% in women and 52% in men. The age-specific analysis among the young (19-49 years), middle-aged (50-74 years) and elderly (≥75 years) yielded cumulative PAFs of 47%, 54% and 13% in women, while the corresponding PAFs in men were 54%, 73% and 14%.

The association between the 17 SNPs included in our study and risk of VTE has scarcely been studied in men and women separately. None of the included SNPs are linked to sex chromosomes, and therefore, the allele frequencies of the included genotypes were similar in men and women. The allele frequencies of our SNPs fit well with those previously reported in populations of European origin (125, 126, 188). Roach et al. studied the association of FVL, F2 and non-O-blood groups with risk of VTE in men and women. They reported similar ORs and PAFs in men and women, with 39% and 35% for non-O, 10% and 8% for FVL, and 4% and 3% for F2, separately. The estimates for FVL were comparable to our findings, but their estimates were larger for F2 and non-O blood type. This could be explained by differences in study design, as the MEGA study is a case-control study with a younger age distribution which could lead to increased risk estimates due to a lower baseline risk of VTE in the control population. A surprising finding in our study was the association between TC2N and increased VTE risk in women, but not in men, with PAF estimates of 11.6% in women compared to 2.1% in men, which could indicate a differential impact of TC2N in men and women. The previous literature on TC2N and risk of VTE has been inconsistent. The first study that identified TC2N as a possible prothrombotic genotype for VTE estimated ORs in three different European case-control studies, and the results varied from 1.08 to 1.30 (189). However, later studies have found little to no association between TC2N and VTE (60, 188, 190). A large meta-analysis of GWAS data

from 18 studies reported an OR of only 1.05 (60), and two studies in women reported no association between TC2N and VTE (188, 190). Therefore, even though our findings indicate that TC2N could play a role as a substantial attributable risk factor in women, this could be a chance finding.

We are not aware of any previous study that has investigated the cumulative PAF of prothrombotic genotypes in men and women separately. Our sex-specific analyses uncovered that the cumulative PAF model explained a larger percentage (52%) of the VTEs in men than in women (38%). We also found that the portion of VTE events attributable to prothrombotic genotypes varied in men and women of different ages. Few previous studies have investigated sex-specific genetic VTE risk in different age groups. In a cross-sectional study, Weingarz et al. studied patients aged >40 years with a first-time VTE, and found a higher prevalence of thrombophilia in men (46.3%) than in women (41.3%) (131). Furthermore, Zöller et al. reported marginally higher standardized incidence ratios in men than in women in a nationwide sibling study of individuals aged 20-60 years (187). However, the observed sex-differences in these studies were not statistically significant. In the MEGA case-control study, Roach et al. hypothesized that the observed higher VTE risk in men compared with women without reproductive risk factors could be explained by a difference in genetic risk (111). However, further study of FVL, prothrombin and ABO-blood group uncovered only slightly higher risk estimates in men than in women in the same population (120). When determining cumulative PAF, we applied the same model as in paper II, (191) as the SNPs included in this model were in accordance with earlier research on prothrombotic genotypes and VTE (126, 129, 190). Alternatively, we could have based our model on the SNPs with the highest individual PAF estimates in our sex-specific analysis. However, if we constructed our model based solely on our own data, this could render the results susceptible to overestimation of the genetic association, more commonly known as winner's curse (192). We strived to avoid this by ensuring that the SNPs selected for the cumulative model corresponded well with previous literature on the VTE risk and did not select SNPs for the model based solely on the HRs in our own sample.

In individuals aged <50 years, we observed a slightly lower cumulative PAF in women (47%) than in men (54%). As a proportion of the VTEs in young women would be attributed to

female reproductive risk factors (52, 88, 120, 193) this could likely explain why the proportion attributed to genetic factors was lower in young women than in young men. Among the middle-aged (50-75 years), we found that the cumulative PAF of prothrombotic genotypes was noticeably higher in men (73%) than in women (54%) Bearing in mind that reproductive risk factors are rare in the middle-aged (194), and that post-menopausal hormonal therapy use has decreased in the Norwegian population in the last decades (195), it is unlikely that the differences in PAF in this age group is due to reproductive risk factors. One possibility is that genetically susceptible women experience VTE earlier in the lifespan than men with a similar genetic profile due to the additional effect of reproductive risk factors. Furthermore, genetically susceptible men could be more vulnerable in middle-age due to an additive effect of other risk factors such as body height (53, 54) and obesity (62). This hypothesis is supported by the "catch-up" effect observed in middle-aged men when studying the sex-specific lifetime risk in men and women separately (193). Finally, the comparatively low PAF of prothrombotic genotypes observed in the elderly (women: 13%, men: 14%) could be explained by further erosion of susceptible individuals in both sexes, in addition to the higher frequency of other major risk factors for VTE in the elderly, such as cancer, surgery and immobility (45). The increased proportion of prothrombotic genetic risk factors among young individuals experiencing incident VTE events compared to the proportion among elderly individuals has previously been recounted in other studies (131, 187, 191), and our findings further support that people with a high genetic risk usually experience VTE earlier in life, regardless of sex.

5.2.3 Body height and VTE in men and women

In paper IV, using a population-based cohort consisting of the HUNT and Tromsø studies, we confirmed the association between taller stature and increased risk of VTE in men and women. Additionally, we investigated whether differences in body height in men and women could account for differences in risk of VTE. In the middle aged, men had a much higher risk of VTE than women, but the difference in risk of VTE disappeared after adjustment for body height. Among those aged 19-49 and ≥75 years, the VTE risk was comparable in men and women before accounting for body height, but a higher risk was found in women after adjustment. Our results imply that differences in body height impacts the VTE risk in men versus women in all age groups.

Previous studies have established that taller stature is a risk factor for VTE in men (53, 54, 63, 64), but the results have been less convincing in women (53, 54, 63). The Tromsø study found a strong association between increasing body height and VTE in men, but a less distinct association in women (53). Correspondingly, the MEGA study, reported a linear relationship between VTE risk and body height in men, while a much weaker association was reported in women (54). The observed weak association between body height and VTE seen in women in these studies could be due to limited sample size. There are other studies that have shown a robust association between VTE risk and taller stature in women. The Iowa Women's Health study (136), a cohort which consisted solely of women aged 55-69 years, reported a near two-fold increased risk of VTE in women ≥167.6 cm compared to those <157.5 cm. Additionally, the LITE cohort uncovered that longer leg-length was associated with VTE in both men and women aged ≥45 years (134). Furthermore, Zöller et al. reported a strong association between taller stature and VTE risk in both sexes in a Swedish registry-based study (56). The study found a threefold increase in VTE risk in men ≥190 cm compared to men <160 cm, and in women ≥185 cm compared to women <155 cm. Similarly, we confirmed that increasing body height is a risk factor for first-time VTE in both men and women in a large cohort with objectively assessed body height and VTE events, and a wide age span.

The possibility that body height could add more to the VTE risk in men than in women due to their tendency to achieve a taller stature has been explored once before. In the Danish

DCH study (64), which consisted of middle-aged men and women at baseline, the crude IR of VTE was 55% higher in men versus women but was reduced to 18% lower in men versus women after adjustment for difference in body height. Since men are known to have a higher risk of VTE than women among the middle-aged (193), and most studies reporting a higher risk of VTE in men have consisted of middle-aged participants at baseline (113, 120, 196, 197), we wanted to investigate the effect of body height on the VTE risk in men versus women in the young, middle-aged and elderly population. In agreement with the DCH study, we found a higher risk of VTE in middle-aged men compared to women, which diminished after adjustment for body height. In the younger population, men had a lower risk of VTE before adjustment for body height, and this association was further strengthened after body height adjustment. Among the elderly, there was no difference between men and women before body height adjustment, but the VTE risk was higher in women than in men after adjustment, which indicates that taller stature contributes to increase the risk of VTE more in men than in women in this age group as well. Overall, our findings suggest that the risk of VTE is mediated through body height to a greater degree in men than in women across the entire lifespan.

The relationship between body height and VTE has been investigated in a Mendelian randomization study, which found that SNPs linked with taller stature were associated with increased VTE risk, strongly indicating that body height is a causal risk factor for VTE (198). The pathophysiological mechanisms that cause the increased risk of VTE in taller stature is not fully known. Zöller et al. used a co-sibling design to display that the association between body height and VTE was not affected by familial genetic or environmental risk factors (56). Furthermore, the LITE cohort reported that markers of inflammation and hypercoagulability did not mediate the association between body height and VTE (196), and although height is associated with increased risk of cancer, the strong association between height and unprovoked VTE supports that the relationship is not explained by cancer-related VTE (53). Several hypotheses for why body height increases the risk of VTE have been presented. Lutsey et al. established that leg length was a risk factor of VTE independent of body height, while body height was not associated with VTE risk after accounting for leg length (134). Taller people could have a higher number of venous valves in their legs, which is a common point of origin for venous thrombi (134, 199). Taller people have greater venous surface area and increased venous pressure than shorter individuals which could lead to venous stasis (200,

201). Lastly, there are some genetic anomalies that are associated with taller stature and increased risk of VTE, like XXY and XYY (135, 202). Unfortunately, we did not have information on these genetic anomalies in our population, but their rarity suggest that they would have minimal impact on the study estimates.

6. Conclusions

Paper I

We found that the estimated lifetime risk of VTE was slightly higher in women than in men when accounting for the competing risk of death. Our simulation study suggested that reproductive risk factors contribute modestly to the estimated lifetime VTE risk in women. Our findings challenge previous studies reporting a twofold higher risk of first-time VTE in men compared to women without reproductive risk factors, and studies reporting a higher proportion of PEs in women than in men.

Paper II

Our findings suggest that 45% to 62% of all VTE events in the population were attributed to known prothrombotic genotypes. The PAF of established prothrombotic genotypes was higher in DVT than in PE, and higher in the young than in the elderly.

Paper III

Our findings in a Norwegian population suggest that 52% and 38% of the VTEs can be attributed to known, common prothrombotic genotypes in men and women, respectively. The proportion of VTE events attributed to genotypes varied across age groups in both sexes and was particularly high among middle-aged men. In the elderly, the PAF of prothrombotic genotypes was similar in men and women.

Paper IV

Taller stature was a risk factor for VTE in men and in women. The risk of VTE in men versus women varied across age groups but was substantially affected by adjustment for body height in all age groups. Our findings suggest that VTE risk is mediated through body height to a larger extent in men than in women in the young, middle-aged and elderly.

7. Final remarks and future perspectives

The aim of this thesis was to expand our knowledge about differences in the risk of VTE in men and women. We found that women had a marginally higher lifetime risk of VTE than men when the competing risk of death was accounted for. Our simulation study indicated that reproductive risk factors have a modest contribution to the lifetime risk of VTE in women. An important issue we did not address is the "lifetime risk" of recurrent VTE in men and women with a first VTE. It has been proposed that men could have up to twice the risk of recurrent VTE compared with women. However, since most recurrence studies have a short follow-up period (<10 years) they have not been able to capture the "life-time" risk of recurrence (for instance, in a woman with a first VTE at age 20, a recurrence at age 55 would not be captured in a study with short follow-up) (112, 179). Interestingly, a case-control study that assessed the association between a remote history of VTE and the development of VTE in older age reported that among men the OR was higher if the remote VTE event happened 10-30 years ago than if it happened more than 30 years ago (OR: 3.17 vs. 2.10). In contrast, among women, the OR was lower if the remote VTE happened 10-30 years ago than if it happened more than 30 years ago (OR: 1.35 vs. 2.28). Additionally, potential confounders like age, body height and BMI have rarely been accounted for, and few studies have taken the higher death rate in men into account when assessing recurrence risk in men versus women. Further research should aim to investigate the lifetime risk of recurrent VTE in men and women in an unselected population of patients with a first VTE.

This thesis has shown that the lifetime risk of VTE in men and women is similar, but that the contribution of VTE-related risk factors could differ in men and women. We found that a larger portion of VTE events in men than in women were attributable to common prothrombotic genotypes, using a 6-SNP-model. However, it is important to note that our study is the first to report such a difference in men and women, and our findings should be further explored in other study populations. Additionally, there could be other genetic risk factors that contribute differently to VTE risk in men and women that we have not addressed in this study.

We confirmed that body height was a risk factor in men and women, and that taller stature mediated a significant proportion of incident VTE events in men. Few studies have

explored the risk of recurrent VTE by body height in men and women, and whether differences in body height can account for some of the reported differences in recurrent VTE risk in men versus women. A case-control study found that the incidence of recurrent VTE was higher in men than in women of the same height (54). The study also reported that body height only explained a small part of the increased recurrence risk in men compared to women. However, the study population was middle-aged, and the average time of follow-up was 5 years. We are not aware of any study that has investigated this in an unselected cohort population with a long follow-up time. Additionally, further studies on the underlying mechanisms of body height and VTE risk, and more widespread use of other proposed anthropometric measurements, like leg length, is of interest.

Lastly, while we have studied the VTE risk in men and women, sex is increasingly understood as a spectrum, rather than the binary understanding that we have explored in this thesis. The effects of VTE risk factors like long-term exogenous hormones and gender-affirming surgery in transmen- and women is a field of research in rapid growth, but as of today, data is still limited (45, 88, 203). More robust data is needed to fully comprehend the VTE risk of all groups in this landscape.

8. References

1. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I22-30.
2. Line BR. Pathophysiology and diagnosis of deep venous thrombosis. Semin Nucl Med. 2001;31(2):90-101.
3. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. The Lancet. 2012;379(9828):1835-46.
4. Goodman LR. In Search of Venous Thromboembolism: The First 2913 Years. American Journal of Roentgenology. 2013;201(4):W576-W81.
5. Macnalty A. The maladies of Mary Queen of Scots. Med Hist. 1961;5(3):203-9.
6. Pugliese SC, Kawut SM. The Post-Pulmonary Embolism Syndrome: Real or Ruse? Ann Am Thorac Soc. 2019;16(7):811-4.
7. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR. Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US. Blood. 2017;130(2):109-14.
8. van Es N, Wells PS, Carrier M. Bleeding risk in patients with unprovoked venous thromboembolism: A critical appraisal of clinical prediction scores. Thromb Res. 2017;152:52-60.
9. Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. Cells. 2022;11(20).
10. Franchini M, Liumbruno GM, Bonfanti C, Lippi G. The evolution of anticoagulant therapy. Blood Transfus. 2016;14(2):175-84.
11. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, Present, and Future. Pharmaceuticals (Basel). 2016;9(3).
12. Riaz IB, Fuentes H, Deng Y, Naqvi SAA, Yao X, Sangaralingham LR, et al. Comparative Effectiveness of Anticoagulants in Patients With Cancer-Associated Thrombosis. JAMA netw. 2023;6(7):e2325283-e.
13. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92-128.
14. White RH. The Epidemiology of Venous Thromboembolism. Circulation. 2003;107(90231):4I--8.
15. Jørgensen CT, Tavoly M, Pettersen HH, Førsund E, Roaldsnes C, Olsen MK, et al. The venous thrombosis registry in Østfold Hospital (TROLL registry) - design and cohort description. Research and Practice in Thrombosis and Haemostasis. 2022;6(5):e12770.
16. Münster AM, Rasmussen TB, Falstie-Jensen AM, Harboe L, Stynes G, Dybro L, et al. A changing landscape: Temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006–2015. Thrombosis Research. 2019;176:46-53.
17. Sørensen HT, Horvath-Puho E, Lash TL, Christiansen CF, Pesavento R, Pedersen L, et al. Heart Disease May Be a Risk Factor for Pulmonary Embolism Without Peripheral Deep Venous Thrombosis. Circulation. 2011;124(13):1435-41.
18. Bikdeli B, Abou Ziki M, Lip G. Pulmonary Embolism and Atrial Fibrillation: Two Sides of the Same Coin? A Systematic Review. Seminars in Thrombosis and Hemostasis. 2017;43(08):849-63.

19. Grimnes G, Isaksen T, Tichelaar YIGV, Brækkan SK, Hansen J-B. Acute infection as a trigger for incident venous thromboembolism: Results from a population-based case-crossover study. Research and Practice in Thrombosis and Haemostasis. 2018;2(1):85-92.
20. DeGeorgia MA, Chimowitz MI, Hepner A, Armstrong WF. Right atrial spontaneous contrast: echocardiographic and clinical features. Int J Card Imaging. 1994;10(3):227-32.
21. Aberg H. Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. Acta Med Scand. 1969;185(5):373-9.
22. Ribeiro DD, Lijfering WM, Van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Pneumonia and risk of venous thrombosis: results from the MEGA study. Journal of Thrombosis and Haemostasis. 2012;10(6):1179-82.
23. Lutsey PL, Norby FL, Alonso A, Cushman M, Chen LY, Michos ED, et al. Atrial fibrillation and venous thromboembolism: evidence of bidirectionality in the Atherosclerosis Risk in Communities Study. J Thromb Haemost. 2018;16(4):670-9.
24. Glynn RJ, Rosner B. Comparison of Risk Factors for the Competing Risks of Coronary Heart Disease, Stroke, and Venous Thromboembolism. American Journal of Epidemiology. 2005;162(10):975-82.
25. Arshad N, Isaksen T, Hansen J-B, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. European Journal of Epidemiology. 2017;32(4):299-305.
26. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular Trends in Occurrence of Acute Venous Thromboembolism: The Worcester VTE Study (1985-2009). The American Journal of Medicine. 2014;127(9):829-39.e5.
27. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. Journal of Thrombosis and Haemostasis. 2007;5(4):692-9.
28. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4):756-64.
29. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the Incidence of Deep Vein Thrombosis and Pulmonary Embolism. Archives of Internal Medicine. 1998;158(6):585.
30. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011;171(9):831-7.
31. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime Risks of Cardiovascular Disease. New England Journal of Medicine. 2012;366(4):321-9.
32. Heit JA, Ashrani AA, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thrombosis and Haemostasis. 2017;117(02):390-400.
33. Arshad N, Bjøri E, Hindberg K, Isaksen T, Hansen JB, Braekkan SK. Recurrence and mortality after first venous thromboembolism in a large population-based cohort. J Thromb Haemost. 2017;15(2):295-303.
34. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med. 2013;126(9):832.e13-21.

35. Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous Thromboembolism: Advances in Diagnosis and Treatment. Jama. 2018;320(15):1583-94.
36. Barco S, Mahmoudpour SH, Valerio L, Klok FA, Münzel T, Middeldorp S, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med. 2020;8(3):277-87.
37. Spencer FA, Emery C, Joffe SW, Pacifico L, Lessard D, Reed G, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolysis. 2009;28(4):401-9.
38. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. Journal of Thrombosis and Haemostasis. 2005;3(8):1611-7.
39. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3(23):3898-944.
40. Kahn SR. The post-thrombotic syndrome. Hematology Am Soc Hematol Educ Program. 2016;2016(1):413-8.
41. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jørgensen LP. Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism. Thromb Res. 2018;164:170-6.
42. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(1):1801915.
43. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-731.
44. Yvonne ME-V, Suzanne CC, Anton Vonk N, Marion D, Piotr P, Albert TAM, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J. 2017;49(2):1601792.
45. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nature Reviews Cardiology. 2023;20(4):248-62.
46. Periayah MH, Halim AS, Mat Saad AZ. Mechanism Action of Platelets and Crucial Blood Coagulation Pathways in Hemostasis. Int J Hematol Oncol Stem Cell Res. 2017;11(4):319-27.
47. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest. 2002;122(4):1440-56.
48. Mackman N. Triggers, targets and treatments for thrombosis. Nature. 2008;451(7181):914-8.
49. Mackman N. New insights into the mechanisms of venous thrombosis. Journal of Clinical Investigation. 2012;122(7):2331-6.
50. Mackman N. Role of tissue factor in hemostasis, thrombosis, and vascular development. Arterioscler Thromb Vasc Biol. 2004;24(6):1015-22.
51. Rosendaal F. Venous thrombosis: a multicausal disease. The Lancet. 1999;353(9159):1167-73.
52. Heit JA. Epidemiology of venous thromboembolism. Nature Reviews Cardiology. 2015;12(8):464-74.

53. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body Height and Risk of Venous Thromboembolism: The Tromso Study. American Journal of Epidemiology. 2010;171(10):1109-15.
54. Flinterman LE, Van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. Journal of Thrombosis and Haemostasis. 2015;13(4):548-54.
55. Severinsen MT, Johnsen SP, Tjønneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: A Danish follow-up study. European Journal of Internal Medicine. 2010;21(4):268-72.
56. Zöller B, Ji J, Sundquist J, Sundquist K. Body Height and Incident Risk of Venous Thromboembolism. Circulation: Cardiovascular Genetics. 2017;10(5).
57. Roetker NS, Armasu SM, Pankow JS, Lutsey PL, Tang W, Rosenberg MA, et al. Taller height as a risk factor for venous thromboembolism: a Mendelian randomization meta-analysis. Journal of Thrombosis and Haemostasis. 2017;15(7):1334-43.
58. Zöller B. Genetics of venous thromboembolism revised. Blood. 2019;134(19):1568-70.
59. Zöller B, Svensson PJ, Dahlbäck B, Lind-Hallden C, Hallden C, Elf J. Genetic risk factors for venous thromboembolism. Expert Rev Hematol. 2020;13(9):971-81.
60. Lindstrom S, Wang L, Smith EN, Gordon W, Van Hylckama Vlieg A, De Andrade M, et al. Genomic and Transcriptomic Association Studies Identify 16 Novel Susceptibility Loci for Venous Thromboembolism. Blood. 2019:blood.201900043.
61. Zöller B, Ohlsson H, Sundquist J, Sundquist K. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. Thrombosis and Haemostasis. 2013;109(03):458-63.
62. Borch KH, Nyegaard C, Hansen J-B, Mathiesen EB, Njølstad I, Wilsgaard T, et al. Joint Effects of Obesity and Body Height on the Risk of Venous Thromboembolism. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011;31(6):1439-44.
63. Pomp ER, Le Cessie S, Rosendaal FR, Doggen CJM. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. British Journal of Haematology. 2007;139(2):289-96.
64. Severinsen MT, Overvad K, Johnsen SP, Dethlefsen C, Madsen PH, Tjønneland A, et al. Genetic susceptibility, smoking, obesity and risk of venous thromboembolism. British Journal of Haematology. 2010;149(2):273-9.
65. Horsted F, West J, Grainge MJ. Risk of Venous Thromboembolism in Patients with Cancer: A Systematic Review and Meta-Analysis. PLOS Medicine. 2012;9(7):e1001275.
66. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-23.
67. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, et al. Cardiovascular Risk Factors Associated With Venous Thromboembolism. JAMA Cardiology. 2019;4(2):163.
68. Mahmoodi BK, Cushman M, Anne Næss I, Allison MA, Bos WJ, Brækkan SK, et al. Association of Traditional Cardiovascular Risk Factors With Venous Thromboembolism: An Individual Participant Data Meta-Analysis of Prospective Studies. Circulation. 2017;135(1):7-16.
69. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. Circulation. 2012;125(17):2092-9.

70. Bjøri E, Johnsen HS, Hansen JB, Brækkan SK. Hospitalization as a trigger for venous thromboembolism - Results from a population-based case-crossover study. Thromb Res. 2019;176:115-9.
71. Yuan S, Bruzelius M, Xiong Y, Håkansson N, Åkesson A, Larsson SC. Overall and abdominal obesity in relation to venous thromboembolism. Journal of Thrombosis and Haemostasis. 2021;19(2):460-9.
72. Borch KH, Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, et al. Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol. 2010;30(1):121-7.
73. Braekkan SK, Siegerink B, Lijfering WM, Hansen JB, Cannegieter SC, Rosendaal FR. Role of obesity in the etiology of deep vein thrombosis and pulmonary embolism: current epidemiological insights. Semin Thromb Hemost. 2013;39(5):533-40.
74. Faber DR, de Groot PG, Visseren FL. Role of adipose tissue in haemostasis, coagulation and fibrinolysis. Obes Rev. 2009;10(5):554-63.
75. Horvei LD, Grimnes G, Hindberg K, Mathiesen EB, Njølstad I, Wilsgaard T, et al. C-reactive protein, obesity, and the risk of arterial and venous thrombosis. J Thromb Haemost. 2016;14(8):1561-71.
76. Frischmuth T, Hindberg K, Aukrust P, Ueland T, Braekkan SK, Hansen JB, et al. Elevated plasma levels of plasminogen activator inhibitor-1 are associated with risk of future incident venous thromboembolism. J Thromb Haemost. 2022;20(7):1618-26.
77. Anderson FA, Spencer FA. Risk Factors for Venous Thromboembolism. Circulation. 2003;107(23_suppl_1):9I--16.
78. Gangireddy C, Rectenwald JR, Upchurch GR, Wakefield TW, Khuri S, Henderson WG, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. Journal of Vascular Surgery. 2007;45(2):335-42.e1.
79. Agnelli G. Prevention of Venous Thromboembolism in Surgical Patients. Circulation. 2004;110(24_suppl_1):IV-4-IV-12.
80. Hansrani V, Khanbhai M, McCollum C. The Prevention of Venous Thromboembolism in Surgical Patients. Adv Exp Med Biol. 2017;906:1-8.
81. Heit JA, Melton LJ, 3rd, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc. 2001;76(11):1102-10.
82. Pottier P, Hardouin JB, Lejeune S, Jolliet P, Gillet B, Planchon B. Immobilization and the risk of venous thromboembolism. A meta-analysis on epidemiological studies. Thromb Res. 2009;124(4):468-76.
83. Scheres LJJ, Brekelmans MPA, Beenen LFM, Buller HR, Cannegieter SC, Middeldorp S. Sex-specific differences in the presenting location of a first venous thromboembolism. J Thromb Haemost. 2017;15(7):1344-50.
84. Abou-Ismail MY, Citla Sridhar D, Nayak L. Estrogen and thrombosis: A bench to bedside review. Thrombosis Research. 2020;192:40-51.
85. Rosing J, Middeldorp S, Curvers J, Thomassen MCLG, Nicolaes GA, Meijers JC, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. The Lancet. 1999;354(9195):2036-40.
86. Middeldorp S, Meijers JC, van den Ende AE, van Enk A, Bouma BN, Tans G, et al. Effects on coagulation of levonorgestrel- and desogestrel-containing low dose oral contraceptives: a cross-over study. Thromb Haemost. 2000;84(1):4-8.

87. Tans G, Curvers J, Middeldorp S, Thomassen MC, Meijers JC, Prins MH, et al. A randomized cross-over study on the effects of levonorgestrel- and desogestrel-containing oral contraceptives on the anticoagulant pathways. Thromb Haemost. 2000;84(1):15-21.
88. Scheres LJJ, Van Hylckama Vlieg A, Cannegieter SC. Sex-specific aspects of venous thromboembolism: What is new and what is next? Research and Practice in Thrombosis and Haemostasis. 2022;6(4):e12722.
89. Morimont L, Haguet H, Dogné J-M, Gaspard U, Douxfils J. Combined Oral Contraceptives and Venous Thromboembolism: Review and Perspective to Mitigate the Risk. Frontiers in Endocrinology. 2021;12.
90. Jordan WM, Anand JK. PULMONARY EMBOLISM. The Lancet. 1961;278(7212):1146-7.
91. de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014;2014(3):CD010813.
92. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. Bmj. 2009;339:b2921.
93. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Bmj. 2009;339:b2890.
94. Glisic M, Shahzad S, Tsoli S, Chadni M, Asllanaj E, Rojas LZ, et al. Association between progestin-only contraceptive use and cardiometabolic outcomes: A systematic review and meta-analysis. Eur J Prev Cardiol. 2018;25(10):1042-52.
95. Rovinski D, Ramos RB, Fighera TM, Casanova GK, Spritzer PM. Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis. Thrombosis Research. 2018;168:83-95.
96. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.
97. Holmegard HN, Nordestgaard BG, Schnohr P, Tybjaerg-Hansen A, Benn M. Endogenous sex hormones and risk of venous thromboembolism in women and men. J Thromb Haemost. 2014;12(3):297-305.
98. Scheres LJJ, Van Hylckama Vlieg A, Ballieux BEPB, Fauser BCJM, Rosendaal FR, Middeldorp S, et al. Endogenous sex hormones and risk of venous thromboembolism in young women. Journal of Thrombosis and Haemostasis. 2019;17(8):1297-304.
99. Barco S, Nijkeuter M, Middeldorp S. Pregnancy and Venous Thromboembolism. Seminars in Thrombosis and Hemostasis. 2013;39(05):549-58.
100. Virkus RA, Løkkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard Ø. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb Haemost. 2011;106(2):304-9.
101. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus. 2012;28(3):144-6.
102. Gariani K, Hugon-Rodin J, Philippe J, Righini M, Blondon M. Association between polycystic ovary syndrome and venous thromboembolism: A systematic review and meta-analysis. Thrombosis Research. 2020;185:102-8.

103. Svartberg J, Brækkan SK, Laughlin GA, Hansen J-B. Endogenous sex hormone levels in men are not associated with risk of venous thromboembolism: the Tromsø study. European Journal of Endocrinology. 2009;160(5):833-8.
104. Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation. 2019;139(11):1461-2.
105. Scheres LJJ, Selier NLD, Nota NM, van Diemen JJK, Cannegieter SC, den Heijer M. Effect of gender-affirming hormone use on coagulation profiles in transmen and transwomen. J Thromb Haemost. 2021;19(4):1029-37.
106. Johansson M, Johansson L, Lind M. Incidence of venous thromboembolism in northern Sweden (VEINS): a population-based study. Thromb J. 2014;12(1):6.
107. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. The American Journal of Medicine. 2004;117(1):19-25.
108. Oger E. Incidence of Venous Thromboembolism: A Community-based Study in Western France. Thrombosis and Haemostasis. 2000;83(05):657-60.
109. Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromsø study. Journal of Thrombosis and Haemostasis. 2008;6(11):1851-7.
110. Kort D, Van Rein N, Van Der Meer FJM, Vermaas HW, Wiersma N, Cannegieter SC, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. Journal of Thrombosis and Haemostasis. 2017;15(12):2352-60.
111. Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex Difference in Risk of Second but Not of First Venous Thrombosis. Circulation. 2014;129(1):51-6.
112. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ. 2019;366:l4363.
113. Roach RE, Lijfering WM, Tait RC, Baglin T, Kyrle PA, Cannegieter SC, et al. Sex difference in the risk of recurrent venous thrombosis: a detailed analysis in four European cohorts. J Thromb Haemost. 2015;13(10):1815-22.
114. Tormene D, Ferri V, Carraro S, Simioni P. Gender and the Risk of Venous Thromboembolism. Seminars in Thrombosis and Hemostasis. 2011;37(03):193-8.
115. Rossello X, González-Del-Hoyo M. Survival analyses in cardiovascular research, part II: statistical methods in challenging situations. Revista Española de Cardiología (English Edition). 2022;75(1):77-85.
116. World Health O. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2019 2019.
117. Norway S. Age-specific death rates for males and females. 2022. StatBank source table 05381. Available from: https://www.ssb.no/en/statbank/sq/100922222024 [cited 2024 27.01].
118. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010;8(10):2105-12.

119. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, et al. Lifetime Risk of Venous Thromboembolism in Two Cohort Studies. The American Journal of Medicine. 2016;129(3):339.e19-.e26.
120. Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. Journal of Thrombosis and Haemostasis. 2014;12(10):1593-600.
121. Abildgaard U. Olav Egeberg - arvelig antitrombinmangel og trombofili. Tidsskrift for den Norske Lægeforening. 2001;121(5).
122. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nat Rev Cardiol. 2014;11(3):140-56.
123. Larsen TB, Sørensen HT, Skytthe A, Johnsen SP, Vaupel JW, Christensen K. Major Genetic Susceptibility for Venous Thromboembolism in Men: A Study of Danish Twins. Epidemiology. 2003;14(3):328-32.
124. Crous-Bou M, Harrington LB, Kabrhel C. Environmental and Genetic Risk Factors Associated with Venous Thromboembolism. Semin Thromb Hemost. 2016;42(8):808-20.
125. Morange P-E, Suchon P, Trégouët D-A. Genetics of Venous Thrombosis: update in 2015. Thrombosis and Haemostasis. 2015;114(11):910-9.
126. Heit JA, Cunningham JM, Petterson TM, Armasu SM, Rider DN, De Andrade M. Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism. Journal of Thrombosis and Haemostasis. 2011;9(6):1133-42.
127. Morange PE, Tregouet DA. Lessons from genome-wide association studies in venous thrombosis. Journal of Thrombosis and Haemostasis. 2011;9:258-64.
128. Trégouët D-A, Morange P-E. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. British Journal of Haematology. 2018;180(3):335-45.
129. de Haan HG, Bezemer ID, Doggen CJM, Le Cessie S, Reitsma PH, Arellano AR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. Blood. 2012;120(3):656-63.
130. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. Blood. 2012;120(5):933-46.
131. Weingarz L, Schwonberg J, Schindewolf M, Hecking C, Wolf Z, Erbe M, et al. Prevalence of thrombophilia according to age at the first manifestation of venous thromboembolism: results from the MAISTHRO registry. British Journal of Haematology. 2013;163(5):655-65.
132. Zöller B, Ohlsson H, Sundquist J, Sundquist K. A sibling based design to quantify genetic and shared environmental effects of venous thromboembolism in Sweden. Thrombosis Research. 2017;149:82-7.
133. Krieg S, Kostev K, Luedde M, Krieg A, Luedde T, Roderburg C, et al. The association between the body height and cardiovascular diseases: a retrospective analysis of 657,310 outpatients in Germany. European Journal of Medical Research. 2022;27(1).
134. Lutsey PLC, Mary, Heckbert SR, Tang W, Folsom AR. Longer legs are associated with greater risk of incident venous thromboembolism independent of total body height. Thrombosis and Haemostasis. 2011;106(07):113-20.

135. Zöller B, Ji J, Sundquist J, Sundquist K. High Risk of Venous Thromboembolism in Klinefelter Syndrome. Journal of the American Heart Association. 2016;5(5):e003567.
136. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR, et al. Correlates and Consequences of Venous Thromboembolism: The Iowa Women's Health Study. American Journal of Public Health. 2010;100(8):1506-13.
137. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø Study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scandinavian Journal of Public Health. 2022;50(7):919-29.
138. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: The Tromso Study. International Journal of Epidemiology. 2012;41(4):961-7.
139. Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, et al. Cohort Profile: The HUNT Study, Norway. International Journal of Epidemiology. 2013;42(4):968-77.
140. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.
141. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
142. Sode BF, Allin KH, Dahl M, Gyntelberg F, Nordestgaard BG. Risk of venous thromboembolism and myocardial infarction associated with factor V Leiden and prothrombin mutations and blood type. Cmaj. 2013;185(5):E229-37.
143. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016;133(6):601-9.
144. Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. Journal of Thrombosis and Haemostasis. 2015;13(3):390-7.
145. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496.
146. Zapata-Diomedi B, Barendregt JJ, Veerman JL. Population attributable fraction: names, types and issues with incorrect interpretation of relative risks. British Journal of Sports Medicine. 2018;52(4):212-3.
147. Szklo M, Nieto FJ. Epidemiology : beyond the basics. Burlington, Massachusetts: Jones & Bartlett Learning; 2019.
148. Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. European Journal of Epidemiology. 2014;29(8):551-8.
149. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.
150. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. Modern Epidemiology. Philadelphia: Wolters Kluwer / Lippincott Williams & Wilkins; 2021.
151. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet. 2002;359(9303):341-5.
152. Rothman KJ. Epidemiology : an introduction. Oxford: Oxford University Press; 2002.

153. Cai J, Kim S. Case-cohort design in hematopoietic cell transplant studies. Bone Marrow Transplantation. 2022;57(1):1-5.
154. Lu CY. Observational studies: a review of study designs, challenges and strategies to reduce confounding. Int J Clin Pract. 2009;63(5):691-7.
155. Patino CM, Ferreira JC. Internal and external validity: can you apply research study results to your patients? Jornal Brasileiro de Pneumologia. 2018;44(3):183-.
156. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016;6(11):e012832.
157. Howe LD, Tilling K, Galobardes B, Lawlor DA. Loss to Follow-up in Cohort Studies: Bias in Estimates of Socioeconomic Inequalities. Epidemiology. 2013;24(1):1-9.
158. Søgaard AJ, Selmer R, Bjertness E, Thelle D. The Oslo Health Study: The impact of self-selection in a large, population-based survey. International Journal for Equity in Health. 2004;3(1).
159. Galea S, Tracy M. Participation Rates in Epidemiologic Studies. Annals of Epidemiology. 2007;17(9):643-53.
160. Åsvold BO, Langhammer A, Rehn TA, Kjelvik G, Grøntvedt TV, Sørgjerd EP, et al. Cohort Profile Update: The HUNT Study, Norway. Int J Epidemiol. 2023;52(1):e80-e91.
161. Morange PE, Trégouët DA. Current knowledge on the genetics of incident venous thrombosis. Journal of Thrombosis and Haemostasis. 2013;11:111-21.
162. Bhatti P, Sigurdson AJ, Wang SS, Chen J, Rothman N, Hartge P, et al. Genetic Variation and Willingness to Participate in Epidemiologic Research: Data from Three Studies. Cancer Epidemiology, Biomarkers & Prevention. 2005;14(10):2449-53.
163. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? Epidemiology. 2006;17(4):413-8.
164. Bjertness E, Sagatun Å, Green K, Lien L, Søgaard AJ, Selmer R. Response rates and selection problems, with emphasis on mental health variables and DNA sampling, in large population-based, cross-sectional and longitudinal studies of adolescents in Norway. BMC Public Health. 2010;10(1).
165. Fernihough A, McGovern ME. Physical stature decline and the health status of the elderly population in England. Econ Hum Biol. 2015;16:30-44.
166. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Statistics in Medicine. 2004;23(24):3803-20.
167. Keyes KM, Utz RL, Robinson W, Li G. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971-2006. Soc Sci Med. 2010;70(7):1100-8.
168. Arntsen SH, Borch KB, Wilsgaard T, Njølstad I, Hansen AH. Time trends in body height according to educational level. A descriptive study from the Tromsø Study 1979–2016. PLOS ONE. 2023;18(1):e0279965.
169. Drøyvold WB, Nilsen TIL, Krüger Ø, Holmen TL, Krokstad S, Midthjell K, et al. Change in height, weight and body mass index: Longitudinal data from the HUNT Study in Norway. International Journal of Obesity. 2006;30(6):935-9.
170. Mansournia MA, Altman DG. Population attributable fraction. Bmj. 2018;360:k757.
171. Rockhill B, Weinberg CR, Newman B. Population Attributable Fraction Estimation for Established Breast Cancer Risk Factors: Considering the Issues of High Prevalence and Unmodifiability. American Journal of Epidemiology. 1998;147(9):826-33.

172. Wang T, Hosgood HD, Lan Q, Xue X. The Relationship Between Population Attributable Fraction and Heritability in Genetic Studies. Frontiers in Genetics. 2018;9.
173. Witte JS, Visscher PM, Wray NR. The contribution of genetic variants to disease depends on the ruler. Nature Reviews Genetics. 2014;15(11):765-76.
174. Uter W, Pfahlberg A. The application of methods to quantify attributable risk in medical practice. Stat Methods Med Res. 2001;10(3):231-7.
175. Brækkan SK, Hald EM, Mathiesen EB, Njølstad I, Wilsgaard T, Rosendaal FR, et al. Competing Risk of Atherosclerotic Risk Factors for Arterial and Venous Thrombosis in a General Population: The Tromsø Study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012;32(2):487-91.
176. Lind MM, Johansson M, Själander A, Johansson L. Incidence and risk factors of venous thromboembolism in men and women. Thrombosis Research. 2022;214:82-6.
177. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular Risk Factors and Venous Thromboembolism Incidence: The Longitudinal Investigation of Thromboembolism Etiology. Archives of Internal Medicine. 2002;162(10):1182-9.
178. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. International journal of epidemiology. 2012;41(3):861-70.
179. Douketis J, Tosetto A, Marcucci M, Baglin T, Cosmi B, Cushman M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ. 2011;342(feb24 2):d813-d.
180. Folsom AR, Cushman M, Tsai MY, Heckbert SR, Aleksic N. Prospective study of the G20210A polymorphism in the prothrombin gene, plasma prothrombin concentration, and incidence of venous thromboembolism. American Journal of Hematology. 2002;71(4):285-90.
181. Li Y, Bezemer ID, Rowland CM, Tong CH, Arellano AR, Catanese JJ, et al. Genetic variants associated with deep vein thrombosis: the F11 locus. Journal of Thrombosis and Haemostasis. 2009;7(11):1802-8.
182. Goumidi L, Thibord F, Wiggins KL, Li-Gao R, Brown MR, van Hylckama Vlieg A, et al. Association between ABO haplotypes and the risk of venous thrombosis: impact on disease risk estimation. Blood. 2021;137(17):2394-402.
183. Luxembourg B, Miesbach W, Gall H. Factor V Leiden paradox in Factor V Leiden homozygotes – a retrospective cohort study. Hamostaseologie. 2023;43(S 01):T-02-8.
184. Shaya SA, Westrick RJ, Gross PL. Thrombus stability explains the factor V Leiden paradox: a mouse model. Blood Adv. 2019;3(21):3375-8.
185. Van Stralen KJ, Doggen CJM, Bezemer ID, Pomp ER, Lisman T, Rosendaal FR. Mechanisms of the Factor V Leiden Paradox. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28(10):1872-7.
186. Bezemer ID, Van Der Meer FJM, Eikenboom JCJ, Rosendaal FR, Doggen CJM. The Value of Family History as a Risk Indicator for Venous Thrombosis. Archives of Internal Medicine. 2009;169(6):610.
187. Zöller B, Li X, Sundquist J, Sundquist K. Age- and Gender-Specific Familial Risks for Venous Thromboembolism. Circulation. 2011;124(9):1012-20.
188. Bruzelius M, Bottai M, Sabater-Lleal M, Strawbridge RJ, Bergendal A, Silveira A, et al. Predicting venous thrombosis in women using a combination of genetic markers and clinical risk factors. Journal of Thrombosis and Haemostasis. 2015;13(2):219-27.

189. Morange PE, Saut N, Antoni G, Emmerich J, Trégouët DA. Impact on venous thrombosis risk of newly discovered gene variants associated with FVIII and VWF plasma levels. Journal of Thrombosis and Haemostasis. 2011;9(1):229-31.
190. Smith NL, Rice KM, Bovill EG, Cushman M, Bis JC, McKnight B, et al. Genetic variation associated with plasma von Willebrand factor levels and the risk of incident venous thrombosis. Blood. 2011;117(22):6007-11.
191. Evensen LH, Arnesen CAL, Rosendaal FR, Gabrielsen ME, Brumpton BM, Hveem K, et al. The Risk of Venous Thromboembolism Attributed to Established Prothrombotic Genotypes. Thrombosis and Haemostasis. 2022;122(07):1221-30.
192. Jiang T, Gill D, Butterworth AS, Burgess S. An empirical investigation into the impact of winner's curse on estimates from Mendelian randomization. International Journal of Epidemiology. 2022;52(4):1209-19.
193. Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. Eur J Epidemiol. 2022;37(2):195-203.
194. Norwegian Institute of Public Health. Medical Birth register - statistical bank 2023 [Available from: https://shorturl.at/zttrL
195. Eriksen EF, Moen MH, Iversen OE. [Estrogens in menopause – time to change the guidelines?]. Tidsskr Nor Laegeforen. 2018;138(6).
196. Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology. Thrombosis Research. 2016;144:127-32.
197. Schafer K, Goldschmidt E, Oostra D, Fish J, Russell T, Lurie F. The clinical significance of ultra-high D-dimer levels. Journal of Vascular Surgery. 2022;10(1):8-13.
198. Roetker N, Maclehose R, Hoogeveen R, Ballantyne C, Basu S, Cushman M, et al. Prospective Study of Endogenous Hormones and Incidence of Venous Thromboembolism: The Atherosclerosis Risk in Communities Study. Thrombosis and Haemostasis. 2018;118(11):1940-50.
199. Moore HM, Gohel M, Davies AH. Number and location of venous valves within the popliteal and femoral veins – a review of the literature. Journal of Anatomy. 2011;219(4):439-43.
200. Fronek A, Criqui MH, Denenberg J, Langer RD. Common femoral vein dimensions and hemodynamics including Valsalva response as a function of sex, age, and ethnicity in a population study. Journal of Vascular Surgery. 2001;33(5):1050-6.
201. Kugler C, Strunk M, Rudofsky G. Venous pressure dynamics of the healthy human leg. Journal of Vascular Research. 2001;38(1):20-9.
202. Berry ASF, Finucane BM, Myers SM, Abril A, Kirchner HL, Ledbetter DH, et al. Association of Supernumerary Sex Chromosome Aneuploidies With Venous Thromboembolism. JAMA. 2023;329(3):235.
203. Shatzel JJ, Connelly KJ, DeLoughery TG. Thrombotic issues in transgender medicine: A review. Am J Hematol. 2017;92(2):204-8.

Paper I

European Journal of Epidemiology (2022) 37:195–203
https://doi.org/10.1007/s10654-021-00813-w

CARDIOVASCULAR DISEASE

Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death

Carl Arne Løchen Arnesen[1] · Katalin Veres[2] · Erzsébet Horváth-Puhó[2] · John-Bjarne Hansen[1,3] · Henrik Toft Sørensen[2] · Sigrid K. Brækkan[1,3]

Received: 25 May 2021 / Accepted: 30 September 2021 / Published online: 8 November 2021

Abstract

Incidence of venous thromboembolism (VTE) risk varies by age and sex. Some studies have reported overall higher risk in men, especially when VTEs triggered by female reproductive factors are excluded. However, higher mortality rates in men may have led to overestimation of lifetime VTE risk in men compared with women. Therefore, we estimated the lifetime risk of VTE in men and women in a Danish, nationwide cohort, taking into account the competing risk of death. Within the population of Denmark (> 5 million persons), all first-time VTEs occurring in 1995–2016 were identified from the Danish National Patient Registry covering all Danish hospitals. The cumulative incidences of VTE were estimated in men and women with age as timescale, taking into account the competing risk of death. Estimated lifetime risk was defined as cumulative incidence at age 100. In a simulation study, we excluded the proportion of female cases that could be attributed to reproductive risk factors and re-estimated the cumulative incidence. We identified 123,543 incident VTEs. The cumulative incidence of VTE was 1.9% in women and 1.3% in men at age 50, 4.3% in women and 4.4% in men at age 70, and 9.3% in women and 8.1% in men at age 100. After accounting for VTEs attributed to reproductive factors, the corresponding incidences in women were 1.2% at age 50, 3.2% at age 70, and 8.2% at age 100. In conclusion, the estimated lifetime risk of VTE was slightly higher in women than in men when accounting for competing risk of death. Our simulation study suggested that reproductive risk factors contribute modestly to the estimated lifetime VTE risk in women.

Keywords Epidemiology · Estimated life time risk · VTE · DVT · PE · Competing risk of death · Cumulative incidence · Reproductive risk factors

Introduction

Previous studies of venous thromboembolism (VTE) risk by sex have provided inconsistent results, with some studies reporting a higher risk in women [1], some reporting a higher risk in men [2–4], and others finding no difference [5]. Incidence rates of VTE in men and women are also reported to vary with age, and differences in study results for overall VTE in men versus women are likely explained by differences in the age range of the populations under study [2, 3, 6, 7]. In younger age groups (< 50 years) the incidence of VTE is higher in women than in men [7] due to female reproductive risk factors (e.g. oral contraceptives and pregnancy), while in middle-aged persons (50–70 years) the incidence is higher in men than in women [2, 6].

A case–control study of persons aged 18–70 years reported that when female reproductive factors were taken into account, the odds ratio was twofold higher in men than in women [8]. This has led to the hypothesis that men have a higher intrinsic risk of incident VTE than women [8]. However, female reproductive risk factors are mainly present at young age (< 50 years), when the baseline risk of VTE is low, thus resulting in a large relative, but modest absolute

✉ Carl Arne Løchen Arnesen
carl.a.arnesen@uit.no

1 Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT-The Arctic University of Norway, 9037 Tromsø, Norway

2 Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

3 Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

risk increase. To date, no study has assessed VTE risk in men and women over the lifespan, accounting for the contribution of female reproductive risk factors to lifetime risk in women.

The competing risk of death is another factor that can influence VTE risk differences in men and women [9]. Men have a higher mortality rate than women across all age groups [10, 11]. This may result in overestimation of VTE risk in men compared with women, particularly in the older age groups, which have the highest absolute difference in mortality rates by sex [12]. Thus, the apparently higher VTE risk in middle-aged and older men could potentially be explained by differences in mortality rates. We are aware of only one study that assessed the lifetime risk of VTE in men and women, while accounting for the competing risk of death. Using two US cohorts aged 45–85 years, Bell et al. found marginally higher cumulative VTE incidence in women than in men (8.4% vs. 7.7%) [13]. To our knowledge, no study has assessed the age-specific cumulative incidence of VTE in men and women using a nationwide cohort including subjects of all ages and taking into account the competing risk of death.

The aim of this study was to estimate the lifetime risk of VTE, deep vein thrombosis (DVT), and PE among men and women using a Danish nationwide cohort, and accounting for death as a competing event. Furthermore, to examine the hypothesis that the inherent lifetime risk of VTE is higher in men, we simulated how absence of female reproductive risk factors could influence the lifetime risk of VTE in women compared with the lifetime risk in men.

Methods

Setting and study population

Our study was based on data obtained from Danish healthcare and administrative registries. The Danish healthcare system is government-funded and provides all legal residents with free access to health care [14]. Complete individual-level linkage between all health and administrative registries is enabled by the unique 10-digit identification number assigned by the Danish Civil Registration System (CRS) to all legal residents at birth or upon immigration [15]. The Danish National Patient Registry (DNPR), which is linked to the CRS, contains data on more than 99% of all inpatient stays and outpatient visits to Danish hospitals. Each hospitalization or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses coded according the *International Classification of Diseases, Tenth Revision* (ICD-10) [16].

The entire population of Denmark in 1995 ($N = 5{,}306{,}416$) served as the source cohort. Individuals with a history of VTE before 1995 were excluded. The cohort was followed from January 1, 1995 through December 31, 2016. Information on age, sex, date of emigration (when applicable), and death (when applicable) was obtained from the CRS.

Ascertainment of patients with venous thromboembolism

The DNPR was used to identify all inpatients and outpatients with a primary or secondary discharge diagnosis of DVT, PE, splanchnic vein thrombosis, or cerebral vein thrombosis, based on ICD-10 diagnosis codes (listed in Supplementary Table 1), during the period January 1, 1995 through December 31, 2016. In patients experiencing DVT and PE simultaneously, only PE was counted due its greater severity.

Competing risk of death

Non-informative (i.e. independent) censoring is an assumption in the traditional Kaplan–Meier survival analysis. This means that at each time point, subjects who remain in the study should have the same future risk of the disease (i.e. VTE) as those who have dropped out of the study (censored). However, when a person is censored due to death, the risk of VTE is instantly reduced to zero, and the assumption of non-informative censoring is therefore violated. Consequently, a high risk of death will lead to an overestimation of VTE risk, and thus bias the results [17, 18]. The cumulative incidence function (CIF) allows for estimation of the incidence of an outcome while taking competing risk into account. In the competing risk setting, only one type of event can occur. Thus, the occurrence of one event precludes subsequent occurrence of other event types. The sum of the CIF estimates for each separate outcome equals the CIF estimate for the composite outcome comprising all the competing events [17].

Statistical analysis

We characterized the source cohort according to sex and age groups. Person-time of follow-up accrued from inclusion in the cohort until the date of an incident VTE, emigration from Denmark, death, or end of the study period (Dec 31, 2016), whichever occurred first. To estimate incidence rates of VTE and death, the population was divided into five-year age groups ranging from 0–4 to 100 + years. Age was used as the time scale, and the 5-year age groups were modeled as time-varying covariates (*i.e.*, individuals contributed person-time to different age groups as they grew older during the study period). Incidence rates (IRs) with 95% confidence intervals (CIs) for overall VTE, DVT, PE and death were calculated for each 5-year age group by dividing the number of VTEs by the person-time accrued in that specific

age group in men and women separately. These IRs were expressed as number of events per 1000 person-years (PY) at risk.

Cumulative incidence curves with and without death as a competing event were estimated using age as the time scale. Cumulative incidence with death as a censoring event was estimated using the complement of the Kaplan–Meier product limit estimator (1-KM), while the cumulative incidence estimate with death as a competing event was calculated using CIF [19]. The estimated lifetime risk was defined as the CIF-estimate at age 100.

Since the incidence of VTE has increased during the last 20 years [20], we performed sensitivity analyses to investigate potential birth cohort effects in men and women. The study period was divided into 1995–2005 and 2006–2016, and cumulative incidence curves for men and women were created for each interval.

Simulation study to account for female reproductive risk factors

During their lifetimes, most women are exposed to risk factors associated with female reproduction, such as hormonal contraception or pregnancy, which is known to increase the risk of VTE [21]. We therefore wished to simulate how absence of female reproductive risk factors would influence the cumulative incidence of VTE in women. Studies using relative measures have reported a twofold higher risk of VTE in men compared to women without reproductive risk factors [7, 8]. In a nationwide study of Danish women aged 15–49, Lidegaard et al. reported an overall IR of VTE of 4.03 per 10,000 woman-years in the total population [22]. The IR among former or never users of oral contraceptives was 3.01 per 10,000 woman-years, while the IR among current oral contraceptive users was 6.29 per 10,000 woman-years [22]. Based on these rates, the population-attributable fraction (PAF) of oral contraceptives would be 25% in the 15–49-year age group. Similarly, a nationwide Danish study of pregnancy-related VTE in women aged 15–49 reported that the IR among non-pregnant women was 3.6 per 10,000 woman-years, while the IR among pregnant women was 10.7 per 10,000 woman-years [23]. This corresponded to an estimated PAF of pregnancy of 10%. We estimated conservatively that 45% of all VTE cases in the 15–49 age group could be attributed to oral contraceptive use or pregnancy. In our simulation, we therefore randomly treated 45% of the VTE cases in this age group as if they had never occurred (*i.e.*, the proportion of female cases that could be attributed to reproductive risk factors) and re-estimated the CIF of VTE in women. The simulation approach was repeated 10 times, to obtain an average cumulative incidence measure from the 10 simulations.

SAS version 9.4 (SAS Institute Inc. Cary, North Carolina, USA) was used to perform the statistical analyses and the simulation.

Results

Our study cohort consisted of 2,623,180 (49.4%) men and 2,683,236 (50.6%) women. We identified 123,543 individuals with a first-time diagnosis of VTE between January 1, 1995 and December 31, 2016. The baseline distribution of the study population by 5-year age groups in men and women is presented in Fig. 1. Among the VTEs, 73,749 (59.7%) were DVTs and 49,794 (40.3%) were PEs. The proportion of VTEs presenting as PEs was 41.4% in women and 39.1% in men.

Incidence rates of VTE

The overall crude incidence rates of VTE were 1.28 (95% CI 1.27–1.29) per 1000 person-years in women and 1.17 (95% CI 1.16–1.18) per 1000 PY in men. The incidence rates increased with age in both men and women. In the 15–45-year age group, the incidence rates were higher in women than in men, ranging from 0.24 to 0.68 per 1000 PY in women and from 0.07 to 0.62 per 1000 PY in men (Table 1). For persons aged 45 to 80 years, the rates were higher in men than in women (ranges: 0.85–4.16 per 1000 PY in men and 0.79–3.94 per 1000 PY in women). In the oldest age groups (≥ 80 years) the rates were similar or slightly higher in women than in men, ranging from 4.94 to 5.73 per 1000 PY in women and from 4.92 to 4.98 per 1000 PY in men (Table 1). The overall incidence rate of DVT was 0.75 (95% CI 0.74–0.76) per 1000 PY in women and 0.71 (95% CI 0.70–0.72) per 1000 PY in men. The rate of PE was 0.53 (95% CI 0.52–0.54) per 1000 PY in women and 0.46 (95% CI 0.45–0.47) per 1000 PY in men. The incidence rates of DVT and PE followed the same patterns as those observed for overall VTE in men and women across all age groups (Supplementary Tables 1 & 2).

Death rates

Death rates in men and women by 5-year age groups are shown in Fig. 2. The death rates were essentially the same for men and women up to the age of 40 and then were consistently higher in men.

Cumulative incidence of VTE

With the traditional 1-KM approach, the total cumulative incidences of VTE in men and women were 0.2% and 0.6% at age 30, 1.3% and 1.9% at age 50, 4.9% and 4.6% at age

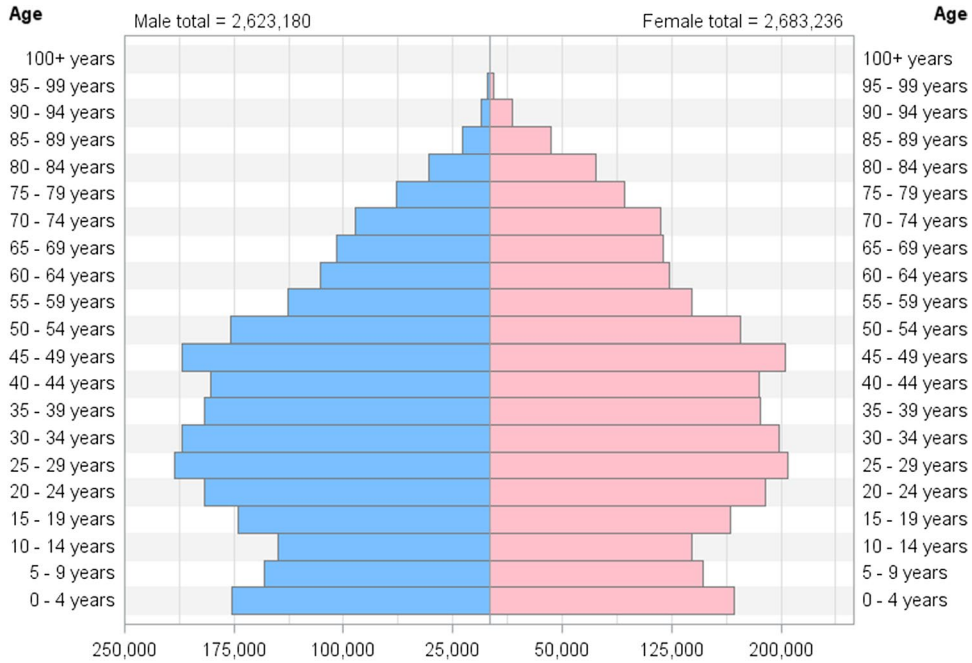


Fig. 1 Distribution of the study population at baseline inclusion in 1995 by sex and five-year age groups

Table 1 Incidence rates per 1000 person-years of venous thromboembolism by five-year age groups in men and women

	Women			Men		
Age (years)	n	Events	IR (95% CI)	n	Events	IR (95% CI)
0–4	167,754	2	0.00 (0.00–0.01)	176,096	0	–
5–9	313,930	5	0.00 (0.00–0.01)	329,681	7	0.01 (0.00–0.01)
10–14	451,067	25	0.01 (0.01–0.02)	472,786	17	0.01 (0.00–0.01)
15–19	614,941	620	0.24 (0.22–0.25)	643,523	194	0.07 (0.06–0.08)
20–24	799,829	1355	0.40 (0.38–0.43)	835,050	461	0.13 (0.12–0.14)
25–29	893,259	1927	0.55 (0.52–0.57)	935,255	706	0.19 (0.18–0.21)
30–34	929,095	2206	0.58 (0.56–0.61)	972,259	1272	0.32 (0.30–0.34)
35–39	971,995	2412	0.60 (0.58–0.62)	1,013,893	1929	0.46 (0.44–0.48)
40–44	1,003,078	2790	0.68 (0.65–0.70)	1,040,689	2652	0.62 (0.60–0.65)
45–49	1,022,809	3266	0.79 (0.77–0.82)	1,058,651	3618	0.85 (0.82–0.88)
50–54	1,002,258	3467	0.85 (0.83–0.88)	1,029,410	4652	1.12 (1.09–1.15)
55–59	925,235	3967	1.05 (1.01–1.08)	935,699	5703	1.50 (1.46–1.54)
60–64	849,920	5082	1.48 (1.44–1.52)	837,997	7029	2.09 (2.04–2.14)
65–69	767,425	6600	2.19 (2.13–2.24)	726,802	7610	2.69 (2.63–2.75)
70–74	671,501	7449	2.98 (2.91–3.05)	594,091	7425	3.44 (3.36–3.51)
75–79	544,360	8002	3.94 (3.86–4.03)	431,649	6416	4.16 (4.06–4.26)
80–84	430,778	7592	4.94 (4.83–5.05)	290,458	4772	4.92 (4.78–5.06)
85–89	296,681	5502	5.59 (5.44–5.74)	159,768	2684	5.58 (5.37–5.79)
90–94	153,877	2477	5.70 (5.47–5.92)	61,578	848	5.52 (5.14–5.89)
95–99	47,600	611	5.73 (5.27–6.18)	13,635	134	4.98 (4.13–5.82)
≥ 100	7179	44	3.65 (2.57–4.73)	1402	13	5.88 (2.68–9.07)
Total	12,864,571	65,401	1.28 (1.27–1.29)	12,560,372	58,142	1.17 (1.16–1.18)

70, and 17.6% and 17.4% at age 100, respectively (Fig. 3a). With the CIF approach, accounting for the competing risk of death, the estimated cumulative incidence of VTE was substantially lowered after the age of 65 in both sexes. The CIF estimates in men and women were 0.2% and 0.6% at age 30, 1.3% and 1.9% at age 50, 4.3% and 4.3% at age 70, and 8.1% and 9.3% at age 100, respectively (Fig. 3b).

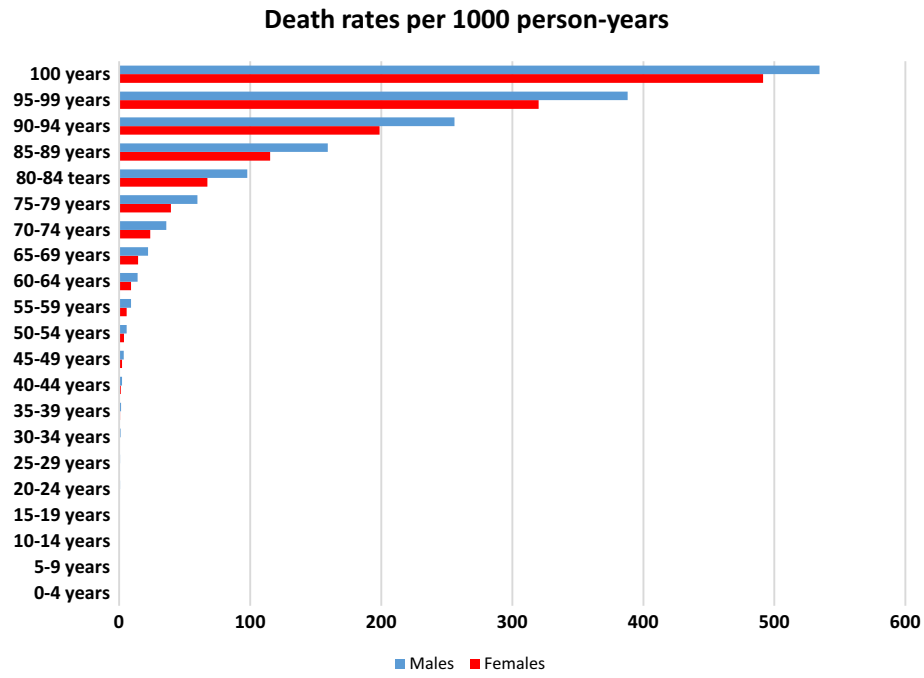


Fig. 2 Death rates in men and women per 1000 person-years

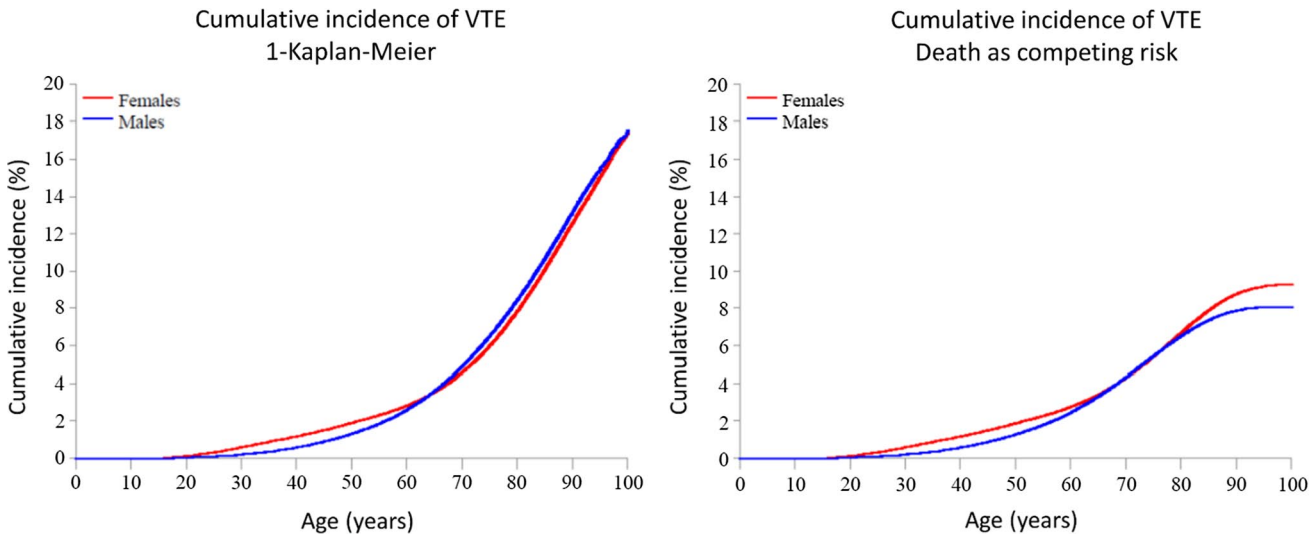


Fig. 3 Cumulative incidence of venous thromboembolism (VTE) by increasing age in men and women, in analyses using traditional censoring (1-Kaplan Meier) (Panel A) and including death as a competing event (Panel B)

In subgroup analyses of DVT and PE, the 1-KM and CIF estimates followed the same patterns as those observed for overall VTE in men and women. With the 1-KM approach, the cumulative incidence of DVT at age 100 was similar in men (10.0%) and women (10.1%) (Fig. 4a). With the CIF approach the estimated cumulative incidence was marginally higher in women (5.4%) than in men (4.9%) (Fig. 4b). A similar pattern was observed for PE: the cumulative incidence at age 100 was 8.1% in women and 8.5% in men in the regular 1-KM analysis, and 4.0% in women and 3.3% in men in the CIF analysis (Fig. 5b).

Our sensitivity analysis showed that the CIF estimates of VTE were higher in both sexes during 2006–2016 compared to 1995–2005. Nevertheless, the patterns were similar in men and women in the two intervals, indicating no gender differences due to birth cohort effects (Supplementary Figs. 1a & b).

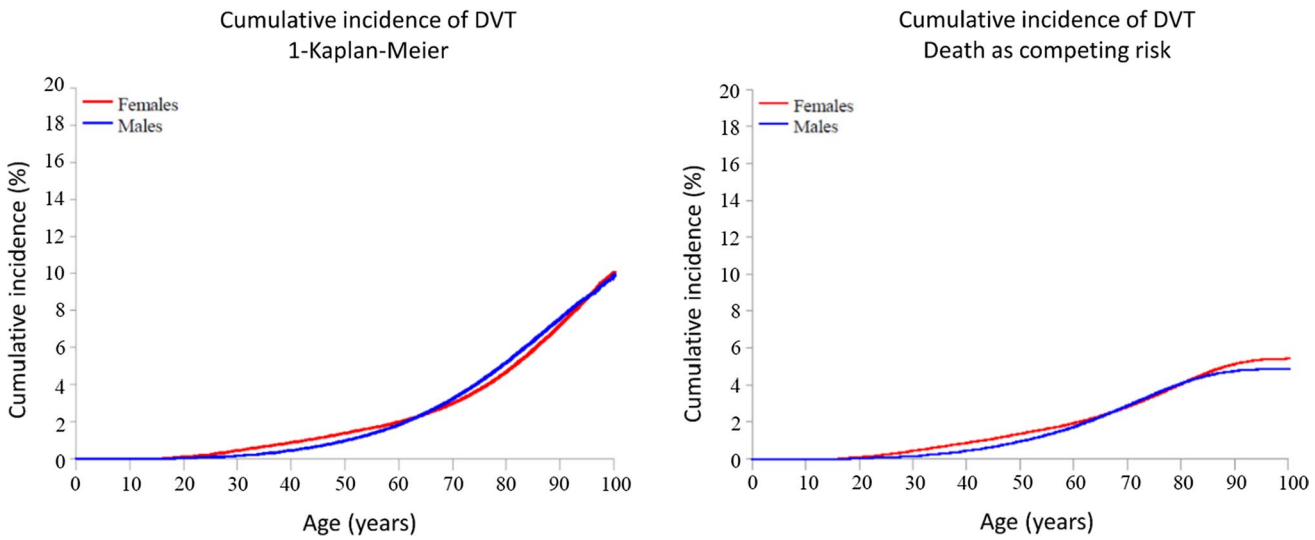


Fig. 4 Cumulative incidence of deep vein thrombosis (DVT) by increasing age in men and women in analyses using traditional censoring (1-Kaplan Meier) (Panel A) and including death as a competing event (Panel B)

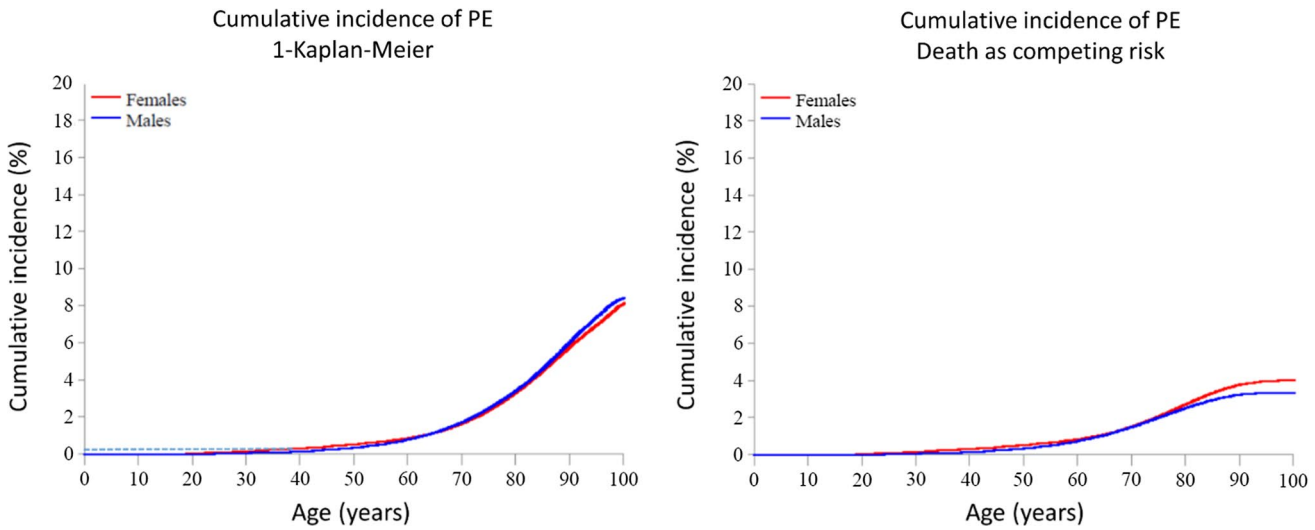


Fig. 5 Cumulative incidence of pulmonary embolism (PE) by increasing age in men and women in analyses using traditional censoring (1-Kaplan Meier) (Panel A) and including death as a competing event (Panel B)

Simulation study of cumulative incidence of VTE to account for female reproductive risk factors

In our simulation study, in which we ignored 45% of VTEs occurring in the female population aged 15–49 years (the proportion of events that could be attributed to female reproductive factors), the cumulative incidence of VTE was 0.5% at age 30, 1.2% at age 50, 3.2% at age 70, and 8.2% at age 100 (Fig. 6) after accounting for the competing risk of death.

Discussion

We assessed age-specific cumulative incidence and estimated lifetime risk of VTE in men and women from the entire Danish population from 1995 to 2016, using an approach accounting for the competing risk of death. The estimated lifetime risk of VTE (cumulative incidence of VTE at age 100), was 9.3% in women and 8.1% in men based on incidence rates from a time period of approximately 20 years. Correspondingly, the estimated lifetime

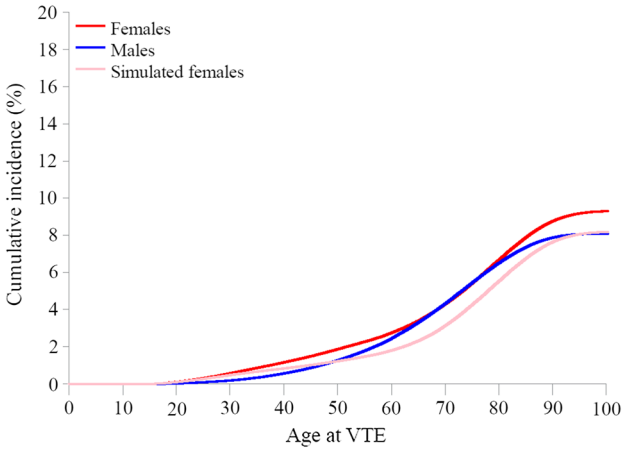


Fig. 6 Cumulative incidence of venous thromboembolism (VTE) by increasing age in men and women including death as a competing risk, and simulated data on females excluding VTE cases caused by reproductive risk factors

risk of DVT was 5.4% in women and 4.9% in men, while the estimated lifetime risk of PE was 4.0% in women and 3.4% in men. In the simulation study, in which we ignored the proportion of VTEs that could be attributed to reproductive risk factors in women, we found that the estimated lifetime risk was similar in men and women (8.1% and 8.2%, respectively). Our results indicate that the overall lifetime risk of VTE is marginally higher in women than in men after accounting for sex differences in death rates. The simulation study suggests that while female reproductive risk factors influence VTE risk in young women, they have a modest influence on their overall lifetime VTE risk.

Previous studies on sex-specific VTE risk have reported that men are either equally [5] or more at risk of VTE than women [24]. Since the incidence rates of VTE vary substantially across different age groups in men and women, the comparison of rates between the sexes is highly dependent on the age range of the population under study [18]. Moreover, when the rate of death is high from causes other than the disease of interest, the incidence rates of the disease are generally overestimated in traditional Kaplan–Meier survival analysis due to competing risks. To compare the lifetime risk of VTE in men and women, we therefore performed our analyses on an unselected nationwide cohort of women and men of all ages, considering death as a competing event. We found that the 1-KM estimate at age 100 was highly overestimated in both sexes. This is likely explained by the high death rate combined with the long follow-up in the study, as these parameters are known to increase the overestimation [12, 18]. As expected, the 1-KM estimate was more overestimated in men than in women due to the higher mortality rate in men.

We are aware of only one previous study that estimated cumulative VTE incidence while accounting for higher death rates in men than in women. Bell et al. estimated the lifetime risk of VTE in a cohort of 19,599 men and women aged 45–85 years with death as a competing risk [13]. In line with our findings, they reported a lifetime risk of VTE at age 85 of 8.4% in women and 7.7% in men [13], indicating that the overall lifetime incidence of VTE is marginally higher in women than in men, after accounting for death as a competing event.

The rapid increase in cumulative incidence observed in women in their early twenties may be explained by exposure to female reproductive risk factors, such as contraception and pregnancy. In men, we observed a steep increase in VTE incidence after age 50. At age 65 the proportion of men and women who had experienced a VTE was similar. A case–control study of persons aged 18–70 reported that the risk of a first VTE was twice as high in men than in women, after excluding females with reproductive risk factors [8]. However, the study included few females without reproductive risk factors, was based on relative measures, and the upper age limit was 70 years. Our study showed that half of all VTEs in the female population occurred after the age of 70, *i.e.*, at an age when women are not exposed to reproductive risk factors. Moreover, only 22% of VTEs in women occurred before age 50. Based on previous literature [22], we estimated that approximately 45% of all VTEs in this age group could be attributed to oral contraceptives and pregnancy. In our simulation, in which we treated the proportion of cases among young women that could be attributed to reproductive risk factors as if they had not occurred, we found that the estimated lifetime risk was 8.2% in women. This was similar to the estimated lifetime risk in men of 8.1%. This indicates that even if VTEs occurring in women due to reproductive risk factors were avoided, the risk of VTE, taking a lifetime perspective, is similar in men and women.

A paper by Scheres et al. [25] based on the MEGA, Hokusai-VTE, and RIETE studies reported sex differences by the anatomical location of first VTE. A higher proportion of women than men presented with PE, with the difference ranging from 3.1 to 8.5 percentage points [25]. Of note, their findings were presented as conditional proportions, and not as absolute risks, which are needed to fully elucidate potential sex differences in presenting location. Like Scheres et al., we found a two-percentage-point higher proportion of PE among women (41.9%) than among men (39.1%) when considering all VTEs in the population. However, when expressed as absolute risks, the estimated lifetime risk was only marginally higher in women than in men for both PE (4.0% vs. 3.4%) and DVT (5.4% vs. 4.9%). Thus, our findings are in line with previous studies showing that the overall

incidence of DVT and PE do not differ greatly in men and women [1, 2, 4, 6, 26].

The main strength of our study was use of an unselected nationwide cohort, which reduced the risks of selection and attrition bias that might occur in more traditional cohort studies. Moreover, VTE diagnoses in Denmark are usually made by trained specialists, and a validation study of DNPR data reported positive predictive values of 86% and 90% for diagnoses of first-time DVT and PE [27], further strengthening our findings. The study cohort consisted mostly of a homogenous Caucasian population, which reduced the likelihood of confounding by ethnicity, but also may limit its generalizability beyond this population. Another concern is that the slight increase in incidence of VTE during recent decades could be different in men and women [20]. However, a Danish study on temporal trends from 2006 to 2015 reported the same number of new VTE cases in men and women [20], and our sensitivity analyses showed that cumulative incidence patterns in men versus women were very similar in the first (1995–2005) and second (2006–2016) intervals of the study period. Unfortunately, we could not follow a closed cohort from birth to death, but estimated lifetime risk in a Nationwide cohort of all ages followed over 20 years. Even though we used age as time scale, included participants within the entire age range, and assessed whether there were sex-differences in cumulative incidence during follow-up, we cannot rule out potential presence of birth cohort effects that could differ in men and women. Another potential weakness of our study is that precise information on pregnancy and oral contraceptive use was not available in our database. However, Lidegaard et al.*'s* studies, which are derived from the same source population, indicated that 35–45% of VTEs in the 15–49 age group could be attributed to reproductive risk factors. Our simulation approach may be justified further by the exposure of the majority of young women either to oral contraceptive use and/or pregnancy during their lifetime. Restriction of the study population to women who were never exposed to such factors would result in a small and extremely selected population, which is unlikely to be representative of young women in general.

In conclusion, we found that when the competing risk of death was taken into account, the estimated lifetime risk of VTE, DVT and PE was marginally higher in women than in men. Furthermore, when VTEs that could be attributed to female reproductive risk factors were accounted for in a simulation study, the estimated lifetime risk of VTE was similar in men and women, indicating that the contribution of reproductive risk factors to the overall lifetime risk of VTE in women is modest. Our findings challenge previous studies reporting a twofold higher risk of first-time VTE in men compared to women without reproductive risk factors, and studies reporting a higher proportion of PEs in women than in men. Finally, our observation of 8–10% estimated lifetime risk of VTE in women and men highlights the importance of improved primary prevention in both sexes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-021-00813-w.

Authors contributions Conception and design: SKB, JBH, HTS. Acquisition of data and data analyses: KV, EHP, CALA, HTS, NS. Interpretation of results: SKB, JBH, HTS, KV, EHT, CALA, NS. Draft of manuscript: CALA, SKB, JBH. Revision of manuscript: HTS, EHP, KV, NS.

Funding Open access funding provided by UiT The Arctic University of Norway (incl University Hospital of North Norway). The Thrombosis Research Center was supported by an independent grant from Stiftelsen K.G. Jebsen during the 2014–2020 period.

Data availability All data were obtained from Danish healthcare and administrative registries.

Code availability SAS version 9.4 (SAS Institute Inc. Cary, North Carolina, USA).

Declarations

Conflict of interest The authors report no conflicts of interest.

References

1. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the worcester VTE study (1985–2009). Am J Med. 2014;127(9):829-39.e5.
2. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117(1):19–25.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism. Arch Intern Med. 1998;158(6):585.
4. Severinsen MT, Johnsen SP, Tjønneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: a Danish follow-up study. Eur J Intern Med. 2010;21(4):268–72.
5. Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Family history of myocardial infarction is an

independent risk factor for venous thromboembolism: the Tromsø study. J Thromb Haemost. 2008;6(11):1851–7.
6. Arshad N, Isaksen T, Hansen J-B, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017;32(4):299–305.
7. Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. J Thromb Haemost. 2014;12(10):1593–600.
8. Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex difference in risk of second but not of first venous thrombosis. Circulation. 2014;129(1):51–6.
9. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496.
10. Denmark S. Deaths and Life Expectancy 2018 [cited 2020 07.02]. Available from: https://www.dst.dk/en/Statistik/emner/befolkning-og-valg/doedsfald-og-middellevetid#.
11. World Health Organization. World Health Statistics 2018: Monitoring health for the SDGs sustainable development goals. Geneva: Geneva: World Health Organization; 2018.
12. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc. 2010;58(4):783–7.
13. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, et al. Lifetime risk of venous thromboembolism in two cohort studies. Am J Med. 2016;129(3):339.e19-e26.
14. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563–91.
15. Frank L. When an entire country is a cohort. Science. 2000;287(5462):2398–9.
16. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish national patient registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–90.
17. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601–9.
18. Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. J Thromb Haemost. 2015;13(3):390–7.
19. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695–706.
20. Münster AM, Rasmussen TB, Falstie-Jensen AM, Harboe L, Stynes G, Dybro L, et al. A changing landscape: temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006–2015. Thromb Res. 2019;176:46–53.
21. Publications UN. Trends in Contraceptive Use Worldwide 2015: United Nations, Department of Economic and Social Affairs, Population Division; 2016.
22. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ. 2009;339:b2890.
23. Virkus RA, Løkkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard Ø. Venous thromboembolism in pregnant and puerperal women in Denmark 1995–2005. A Natl Cohort Study Thromb Haemost. 2011;106(2):304–9.
24. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464–74.
25. Scheres LJJ, Brekelmans MPA, Beenen LFM, Buller HR, Cannegieter SC, Middeldorp S. Sex-specific differences in the presenting location of a first venous thromboembolism. J Thromb Haemost. 2017;15(7):1344–50.
26. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692–9.
27. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish national patient registry: a validation study. BMJ Open. 2016;6(11):e012832.

Paper II

The Risk of Venous Thromboembolism Attributed to Established Prothrombotic Genotypes

Line H. Evensen[1] Carl Arne Løchen Arnesen[1] Frits R. Rosendaal[1,2] Maiken E. Gabrielsen[3] Ben M. Brumpton[3,4] Kristian Hveem[3,5] John-Bjarne Hansen[1,6] Sigrid K. Brækkan[1,6]

[1] Department of Clinical Medicine, Thrombosis Research Center, UiT-The Arctic University of Norway, Tromsø, Norway
[2] Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[3] Department of Public Health and Nursing, K. G. Jebsen Center for Genetic Epidemiology, Norwegian University of Science and Technology, Trondheim, Norway
[4] Clinic of Thoracic and Occupational Medicine, St. Olavs Hospital, University Hospital, Trondheim, Norway
[5] Department of Public Health and Nursing, HUNT Research Center, Norwegian University of Science and Technology, Levanger, Norway
[6] Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

Address for correspondence Sigrid K. Brækkan, PhD, Thrombosis Research Center, Department of Clinical Medicine, UiT The Arctic University of Norway, Postboks 6050 Langnes, 9037 Tromsø, Norway (e-mail: sigrid.brakkan@uit.no).

Thromb Haemost 2022;122:1221–1230.

Abstract

Background The proportion of venous thromboembolism (VTE) events that can be attributed to established prothrombotic genotypes has been scarcely investigated in the general population. We aimed to estimate the proportion of VTEs in the population that could be attributed to established prothrombotic genotypes using a population-based case-cohort.

Methods Cases with incident VTE ($n = 1{,}493$) and a randomly sampled subcohort ($n = 13{,}069$) were derived from the Tromsø Study (1994–2012) and the Nord-Trøndelag Health (HUNT) study (1995–2008). DNA samples were genotyped for 17 single-nucleotide polymorphisms (SNPs) associated with VTE. Hazard ratios with 95% confidence intervals (CIs) were estimated in Cox regression models. Population-attributable fractions (PAFs) with 95% bias-corrected CIs (based on 10,000 bootstrap samples) were estimated using a cumulative model where SNPs significantly associated with VTE were added one by one in ranked order of the individual PAFs.

Results Six SNPs were significantly associated with VTE (rs1799963 [Prothrombin], rs2066865 [FGG], rs6025 [FV Leiden], rs2289252 [F11], rs2036914 [F11], and rs8176719 [ABO]). The cumulative PAF for the six-SNP model was 45.3% (95% CI: 19.7–71.6) for total VTE and 61.7% (95% CI: 19.6–89.3) for unprovoked VTE. The PAF for prothrombotic genotypes was higher for deep vein thrombosis (DVT; 52.9%) than for PE (33.8%), and higher for those aged <70 years (66.1%) than for those aged ≥70 years (24.9%).

Conclusion Our findings suggest that 45 to 62% of all VTE events in the population can be attributed to known prothrombotic genotypes. The PAF of established prothrombotic genotypes was higher in DVT than in PE, and higher in the young than in the elderly.

Keywords
- venous thromboembolism
- single-nucleotide polymorphisms
- risk factors

received
July 2, 2021
accepted after revision
November 13, 2021
published online
January 17, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1698-6717.
ISSN 0340-6245.

Introduction

Venous thromboembolism (VTE) manifests clinically as deep vein thrombosis (DVT) or pulmonary embolism (PE), and is recognized as a multicausal disease that develops in a complex interplay between environmental, acquired, and inherited risk factors.[1] The inheritance of VTE follows a multifactorial non-Mendelian pattern, which indicates polygenic contribution.[2] Since the discovery of antithrombin deficiency in 1965,[3] improved molecular insights and technological advances have led to the identification of more than 50 single-nucleotide polymorphisms (SNPs) associated with VTE risk.[4–9] In a large case–control study, de Haan and colleagues investigated the performance of 31 SNPs for prediction of incident VTE.[10] They found that a parsimonious model comprising the five SNPs most strongly associated with VTE (i.e., rs6025 [FV Leiden], rs1799963 [Prothrombin], rs8176719 [ABO], rs2066865 [FGG], and rs2036914 [F11]) performed as well as the full 31-SNP model, suggesting that a substantial amount of the genetic predisposition of VTE could be attributed to relatively few prothrombotic variants.

Several measures can be used to evaluate the genetic contribution to the development and burden of disease, such as heritability, sibling recurrence risk, impact on the overall genetic variance, or population-attributable fraction (PAF).[11] In a public health perspective, the PAF is of interest, as it reflects the proportion of cases in a population that is attributable to the risk factor, and indicates by what proportion the incidence of disease would decrease if the risk factor could hypothetically be removed.[12] The proportion of VTEs in the population that can be attributed to the already established prothrombotic genotypes has so far been fragmentarily investigated. In a case–control study from 2011, Heit et al reported a joint PAF of 40% for the SNPs F5 (rs6025), F2 (rs1799963), ABO (rs8176719), and ABO (rs2519093).[13] Since then, other prothrombotic genotypes have been identified, and the joint PAF of these genotypes has, to our knowledge, not been assessed in a cohort of unselected VTE patients within a wide age range. The risk of VTE increases exponentially with age,[14] and previous studies have indicated a higher PAF in the young than in the elderly for some individual genotypes.[15] However, the joint PAF of prothrombotic genotypes has not been well quantified and compared between different age groups in the same population.

Previous studies have shown that the FV Leiden (FVL) mutation is associated with a higher risk of DVT than of PE, also referred to as the FVL paradox.[16] To what extent this applies to the other genotypes, and whether the joint PAF of prothrombotic genotypes differs in DVT and PE is not well addressed.

The aim of the present study was to estimate the proportion of VTEs in the population that could be attributed to the established VTE-related SNPs, individually and in a cumulative model. Moreover, we aimed to assess the PAF in different age groups and in clinical phenotypes (DVT and PE).

Methods

Study Population

Participants were recruited from the fourth survey of the Tromsø Study (Tromsø 4, 1994–95) and the second survey of the Nord-Trøndelag Health (HUNT 2, 1995–97) study. These are two Norwegian population-based cohort studies of the inhabitants in Tromsø municipality and Nord-Trøndelag County, respectively. In Tromsø 4, the entire population aged ≥25 years was invited, and 77% (27,158) participated. In HUNT 2, all inhabitants aged ≥20 years were invited and 71% (66,140) participated. Detailed methodologies of the Tromsø Study[17] and the HUNT Study[18] have been published elsewhere.

The participants were followed from the date of enrolment in the respective studies until the date of incident VTE, migration, death, or to the end of follow-up, whichever occurred first. Follow-up ended on December 31, 2012 in the Tromsø Study and on December 31, 2008 in the HUNT Study. The processes of VTE identification and adjudication in the Tromsø Study[19] and the HUNT Study[20] have previously been described in detail. In the Tromsø Study, VTE events were identified by searching the hospital discharge diagnosis registry, the radiology procedure registry, and the autopsy registry at the University Hospital of North Norway. The medical records were reviewed by trained personnel and the adjudication criteria were signs and symptoms of DVT or PE, combined with objective confirmation by a radiological procedure that resulted in treatment unless contraindications were specified. In the HUNT Study, VTE events were identified by searching the discharge diagnosis registry and the radiology procedure registry at two local hospitals (Levanger and Namsos) and the discharge diagnosis registry at the tertiary-care center of the region, St. Olavs Hospital in Trondheim. Two physicians reviewed the medical records and the adjudication criterion for VTE was objective confirmation by a radiological procedure.

The composition of the case–cohort is summarized in ►**Supplementary Fig. S1** (available in the online version). In total, there were 1,493 incident VTE events during follow-up, and these were included as cases in the present study. From the Tromsø and HUNT cohorts, 13,072 individuals without previous VTE were randomly selected for the subcohort. As all participants in the original cohort had an equal chance of being selected for the subcohort, 217 VTE cases were included in the subcohort. Participants who were not officially registered as inhabitants of Tromsø or Nord-Trøndelag at baseline ($n = 3$) were excluded from the study. Both studies were approved by the Regional Committees for Medical and Health Research Ethics, and all participants signed an informed consent form prior to inclusion.

Classification of VTE

All events were classified as either PE (with or without DVT) or isolated DVT, and as provoked or unprovoked based on the presence of provoking factors at the time of diagnosis. In the Tromsø Study, provoking factors were: surgery or trauma (within the previous 8 weeks), 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 for ≥4 days within the previous 14 days), or another provoking factor described by a physician in the medical record (e.g., intravascular catheters). In the HUNT Study, provoking factors were: trauma or surgery, cancer (active malignancy at the time of the event or within 6 months after the event), marked immobilization (paresis, paralysis, prolonged bedrest due to acute medical illness, or >8 hour travel) within the previous 3 months, pregnancy or puerperium at the time of the event, or use of oral contraceptives at the time of the event or up to 1 month prior to the event.

Baseline Measurements

Baseline information in both studies was obtained from physical examinations, blood samples, and self-administered questionnaires. Body height and weight were measured with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg m^{-2}). Information on diabetes and arterial cardiovascular disease (CVD; myocardial infarction, stroke, and angina) was collected via self-report.

Selection of SNPs and Genotyping

Based on current knowledge on the genetics of VTE, 17 SNPs with established associations with VTE risk were selected for genotyping in the present study.[5,6] The Tromsø sample was genotyped using the Sequenom and the TaqMan platforms, as previously described .[21] The HUNT sample was genotyped using the Illumina HumanCoreExome array.

Individuals were classified as carriers (≥1 risk allele) or noncarriers (0 risk alleles), and no differentiation was made between hetero- and homozygous carriers in the analyses. For the SNPs rs4524 (F5), rs2036914 (F11), rs1801020 (F12), rs1039084 (STXBP5), and rs1613662 (GP6), the major allele was defined as the risk allele.[5,6,22,23] For the rs8176719 SNP in the ABO gene, the G allele tags non-O blood type (risk group), while homozygous carriers for deletion at this site are phenotyped as blood type O (reference group).[24]

Statistical Analysis

Statistical analyses were performed with STATA version 15.1 (Stata Corp, College Station, Texas, United States). For each participant, person-years of follow-up were accrued from the date of enrolment in the respective study (the Tromsø Study: 1994–95 and the HUNT Study: 1995–97) to the date of incident VTE, migration, death, or to the end of the study period (the Tromsø Study: December 31, 2012 and the HUNT Study: December 31, 2008).

For each SNP, hazard ratios (HRs) of VTE with 95% confidence intervals (CIs) were estimated in Cox proportional hazards regression models with noncarriers (0 risk alleles) as the reference group. Age was used as the time scale with the age at enrolment defined as entry time, and the age at incident VTE or censoring defined as exit time. The analyses were adjusted for age (as time scale), sex, and BMI. The proportional hazards assumption was evaluated on the basis of Schoenfeld residuals.

Several measures can be used to evaluate the impact of a risk factor on the development and burden of disease. In a public health perspective, the PAF is of large interest, as it expresses the proportion of cases in a population that can be attributed to a risk factor. PAF is also known as the "preventable fraction" as it indicates the proportion by which the incidence of disease would decrease if the risk factor could (hypothetically) be removed and the distribution of all other risk factors remained unchanged.[25,26] For SNPs significantly associated with VTE risk in the Cox regression models, PAFs were calculated using the formula $\frac{p(\mathrm{HR}-1)}{p(\mathrm{HR}-1)+1}$, where p is the prevalence in the population (i.e., the subcohort) and HR is the risk of VTE in carriers compared with noncarriers of the respective risk allele.[25] A cumulative PAF model was constructed by adding SNPs one by one into a combined dichotomous exposure variable (i.e., carriers of ≥1 risk allele of any of the added SNPs were categorized as exposed and those with zero risk alleles were categorized as unexposed). The corresponding PAF for each SNP combination was calculated based on prevalence and estimated HR of VTE for the combined exposure variable. The SNPs were added in order of the size of the individual PAFs, starting with the two SNPs with the highest PAF values. For all PAF estimates, 95% bias-corrected CIs were calculated based on 10,000 bootstrap samples. Separate PAF estimates were calculated for total and unprovoked VTE, for PE and DVT, and by age group (<70 or ≥70 years). Participants with missing information on SNPs included in the PAF model ($n = 185$; 13 cases and 172 in the subcohort) and BMI ($n = 91$; 11 cases and 80 in the subcohort) were excluded from these analyses to have an identical sample at each step. Due to the high-risk allele frequency for the F5 SNP rs4524 (92.4% with ≥1 risk allele), PAF was not estimated for this variant.

Results

The mean age of the study population was 51 ± 17 years (range: 19–97 years). Baseline characteristics of the VTE cases and the subcohort are shown in ►**Table 1**. Mean age, BMI, systolic blood pressure, and prevalence of arterial CVD

Table 1 Baseline characteristics of the venous thromboembolism cases and the subcohort

	VTE cases ($n = 1493$)	Subcohort ($n = 13069$)
Age (y), mean ± SD	61 ± 15	51 ± 17
Sex (female), % (n)	52.9 (790)	52.9 (6,909)
Body mass index (kg/m^2), mean ± SD	27.4 ± 4.4	26.2 ± 4.1
Systolic blood pressure (mm Hg), mean ± SD	145 ± 23	138 ± 22
Arterial cardiovascular disease[a], % (n)	14.3 (213)	8.3 (1,083)
Diabetes, % (n)	4.3 (64)	3.1 (410)

Abbreviations: SD, standard deviation; VTE, venous thromboembolism.
[a]Myocardial infarction, stroke, or angina.

Table 2 Allele frequency and distribution of risk alleles in the venous thromboembolism cases and the subcohort

		VTE cases ($n = 1,493$)[a]			Subcohort ($n = 13,069$)[a]		
Gene	SNP	AF (%)	1 risk allele (%,*n*)	2 risk alleles (%,*n*)	AF (%)	1 risk allele (%,*n*)	2 risk alleles (%,*n*)
F5	rs4524	76.6	36.7 (547)	58.3 (870)	72.9	39.2 (5,122)	53.2 (6,954)
FVL	rs6025	7.7	14.4 (214)	0.5 (8)	3.4	6.5 (854)	0.1 (15)
SERP	rs2227589	9.8	17.2 (257)	1.1 (17)	8.7	15.8 (2,069)	0.8 (107)
C4BPB	rs3813948	7.4	13.7 (205)	0.5 (8)	7.7	14.2 (1,848)	0.6 (78)
KNG1	rs710446	42.1	46.6 (695)	18.8 (281)	41.2	48.4 (6,325)	17.0 (2,224)
FGG	rs2066865	27.3	37.4 (559)	8.6 (128)	24.0	36.3 (4,740)	5.8 (756)
F11	rs2036914	57.3	49.6 (739)	32.5 (484)	53.1	50.2 (6,533)	28.0 (3,646)
F11	rs2289252	43.4	48.8 (727)	19.0 (284)	39.2	47.4 (6,188)	15.5 (2,021)
F12	rs1801020	76.3	34.8 (431)	58.9 (728)	74.4	38.0 (4,865)	55.4 (7,092)
F13	rs5985	28.8	40.5 (496)	8.5 (104)	26.7	39.1 (4,983)	7.1 (907)
STXBP5	rs1039084	53.8	48.1 (718)	29.7 (443)	51.5	50.4 (6,582)	26.3 (3,431)
F2	rs3136520	3.1	5.9 (87)	0.2 (3)	3.0	5.8 (763)	0.1 (16)
F2	rs1799963	1.0	2.1 (31)	–	0.7	1.3 (173)	–
vWF	rs1063857	37.8	48.3 (695)	13.7 (197)	38.1	46.6 (5,489)	14.8 (1,744)
TC2N	rs1884841	44.5	50.7 (755)	19.1 (285)	43.0	48.2 (6,299)	18.9 (2,471)
GP6	rs1613662	86.0	23.2 (346)	74.4 (1,110)	82.6	28.7 (3,749)	68.3 (8,917)
ABO	rs8176719	43.1	51.3 (764)	17.4 (260)	38.3	46.3 (6,027)	15.2 (1,978)

Abbreviations: AF, allele frequency; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism.
[a]Not all participants have data on all SNPs.

and diabetes were higher in VTE cases compared with the subcohort.

The allele frequency and risk allele distribution in cases and the subcohort are shown in ►**Table 2**. With the exception of rs3813948 (C4BPB) and rs1063857 (vWF), the risk allele frequencies for all SNPs were higher among cases. Likewise, the proportions of individuals genotyped with ≥1 risk alleles were higher among the cases for the majority of SNPs. The allele frequencies in the subcohort resembled those previously reported in Caucasian populations.[5,6,9]

The HRs of VTE for the individual SNPs are shown in ►**Table 3**. Of the initially 17 included SNPs, seven were significantly associated with VTE risk. These were (multivariable adjusted HRs): rs6025 (FVL; HR: 2.32, 95% CI: 2.01–2.68), rs4524 (F5; HR: 1.52, 95% CI: 1.20–1.92), rs1799963 (F2; HR: 1.51, 95% CI: 1.05–2.17), rs8176719 (ABO; HR: 1.38, 95% CI: 1.24–1.54), rs2289252 (F11; HR: 1.24, 95% CI: 1.11–1.38), rs2036914 (F11; HR: 1.22, 95% CI: 1.07–1.40), and rs2066865 (FGG; HR: 1.18, 95% CI: 1.06–1.30). For DVT and PE, the risk estimates differed for FVL, which was more strongly associated with DVT (HR: 2.92, 95% CI: 2.46–3.47) than with PE (HR: 1.52, 95% CI: 1.17–1.98).

►**Table 4** shows the individual PAFs for the six SNPs associated with VTE risk, as well as the HRs and prevalence s used in the PAF calculations. Ranked in descending order, the overall proportion of cases in the population attributable to the individual SNPs (i.e., PAF) was 18.9% (95% CI: 10.8–26.4) for rs8176719 (ABO), 14.3% (95% CI: 1.4–26.7) for rs2036914 (F11), 13.1% (95% CI: 3.8–20.3) for rs2289252 (F11), 8.0% (95% CI: 5.3–10.8) for rs6025 (FVL), 6.8% (95% CI: 1.2–10.5) for rs2066865 (FGG), and 0.7% (95% CI: −0.4–1.7) for rs1799963 (F2). The PAF was higher for DVT than for PE for rs8176719 (ABO, 21.2 vs. 15.6%) and for rs6025 (FVL, 11.2 vs. 3.3%). Analyses stratified by age revealed that the PAFs were higher among those aged <70 years for rs8176719 (ABO, 28.7 vs. 10.6%), rs2036914 (F11, 20.4 vs. 9.5%), and rs2066865 (FGG, 11.3 vs. 2.9%), while the estimates for the remaining SNPs were comparable between the age groups (►**Table 5**).

The cumulative PAF estimates are shown in ►**Figs. 1** to **3**. The PAF increased stepwise with the addition of each SNP until five SNPs were added. These SNPs were rs8176719 (ABO), rs2036914 (F11), rs2289252 (F11), rs6025 (FVL), and rs2066865 (FGG). For total VTE, the cumulative PAF for this model was 45.3% (95% CI: 19.7–71.2) (►**Fig. 1A**), while for unprovoked VTE the corresponding PAF was 61.7% (95% CI: 19.6–89.3) (►**Fig. 1B**). The cumulative PAF was higher for DVT (52.9%) than for PE (33.8%). For total VTE, the cumulative PAF was higher in those aged <70 years (66.1%, 95% CI: 25.5–90.3) compared with those aged ≥70 years (24.9%, 95% CI: −13.3–54.6). The HRs that formed the basis for the cumulative PAF models are shown in ►**Supplementary Figs. S2–S4** (available in the online version).

Discussion

In the present study, we estimated the proportion of VTEs in the population that could be attributed to already established prothrombotic genotypes. We found that a combination of six SNPs in a cumulative PAF model accounted for 45% of all VTEs and 62% of all unprovoked VTEs in the general

Table 3 Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for venous thromboembolism by individual single-nucleotide polymorphisms (SNPs)

		Venous thromboembolism			Deep vein thrombosis			Pulmonary embolism		
		0 risk alleles	≥1 risk alleles	HR (95% CI)[a]	0 risk alleles	≥1 risk alleles	HR (95% CI)[a]	0 risk alleles	≥1 risk alleles	HR (95% CI)[a]
Gene	SNP	Events	Events	≥1 vs. 0 risk alleles	Events	Events	≥1 vs. 0 risk alleles	Events	Events	≥1 vs. 0 risk alleles
FVL	rs6025	1,258	221	2.32 (2.01–2.68)	719	159	2.92 (2.46–3.47)	539	62	1.52 (1.17–1.98)
F5	rs4524	75	1,406	1.52 (1.20–1.92)	50	829	1.34 (1.01–1.79)	25	577	1.87 (1.25–2.79)
F2	rs1799963	1,446	30	1.51 (1.05–2.17)	860	15	1.26 (0.76–2.10)	586	15	1.88 (1.13–3.14)
ABO	rs8176719	464	1,015	1.38 (1.24–1.54)	266	612	1.45 (1.26–1.68)	198	403	1.29 (1.09–1.53)
F11	rs2289252	474	1,006	1.24 (1.11–1.38)	283	596	1.23 (1.06–1.41)	191	410	1.25 (1.05–1.48)
F11	rs2036914	265	1,214	1.22 (1.07–1.40)	159	719	1.21 (1.02–1.44)	106	495	1.24 (1.01–1.53)
FGG	rs2066865	799	683	1.18 (1.06–1.30)	468	412	1.21 (1.06–1.38)	331	271	1.13 (0.97–1.33)
GP6	rs1613662	36	1,445	1.16 (0.83–1.62)	18	861	1.39 (0.87–2.22)	18	584	0.93 (0.58–1.49)
F13	rs5985	621	593	1.11 (0.99–1.24)	376	355	1.10 (0.95–1.28)	245	238	1.13 (0.94–1.34)
TC2N	rs1884841	444	1,034	1.11 (0.99–1.24)	265	612	1.10 (0.95–1.27)	179	422	1.12 (0.94–1.34)
SERP	rs2227589	1,212	269	1.09 (0.96–1.25)	728	151	1.02 (0.85–1.21)	484	118	1.20 (0.98–1.47)
STXBP5	rs1039084	327	1,154	1.09 (0.97–1.23)	177	702	1.22 (1.04–1.44)	150	452	0.94 (0.78–1.13)
vWF	rs1063857	543	885	1.03 (0.92–1.15)	326	524	1.02 (0.88–1.17)	217	361	1.05 (0.89–1.24)
F2	rs3136520	1,377	90	1.04 (0.84–1.29)	819	53	1.03 (0.78–1.36)	558	37	1.07 (0.77–1.50)
KNG1	rs710446	516	966	1.02 (0.92–1.13)	309	571	1.00 (0.87–1.15)	207	395	1.05 (0.88–1.24)
F12	rs1801020	78	1,148	0.97 (0.77–1.22)	40	692	1.14 (0.83–1.57)	38	456	0.79 (0.57–1.10)
C4BPB	rs3813948	1,270	211	0.97 (0.84–1.13)	764	115	0.87 (0.72–1.06)	506	96	1.12 (0.90–1.40)

[a]Adjusted for age (as time scale) and sex and body mass index.

Table 4 Population-attributable fraction (PAF) of venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) for individual single-nucleotide polymorphisms (SNPs)

Gene	SNP	HR (95% CI)[a]	Subcohort prevalence[b]	PAF (95% CI)
ALL				
ABO	rs8176719	1.38 (1.23–1.54)	0.62	18.9 (10.8–26.4)
F11	rs2036914	1.21 (1.06–1.39)	0.78	14.3 (1.4–26.7)
F11	rs2289252	1.24 (1.11–1.38)	0.63	13.1 (3.8–20.3)
FVL	rs6025	2.31 (2.00–2.66)	0.07	8.0 (5.3–10.8)
FGG	rs2066865	1.17 (1.06–1.30)	0.42	6.8 (1.2–10.5)
F2	rs1799963	1.54 (1.07–2.21)	0.01	0.7 (−0.4–1.7)
DVT				
ABO	rs8176719	1.44 (1.24–1.66)	0.62	21.2 (10.8–31.5)
F11	rs2036914	1.20 (1.01–1.43)	0.78	13.6 (−2.6–29.1)
F11	rs2289252	1.22 (1.06–1.41)	0.63	12.3 (1.4–23.3)
FVL	rs6025	2.90 (2.44–3.44)	0.07	11.2 (7.9–14.9)
FGG	rs2066865	1.20 (1.05–1.37)	0.42	7.6 (0.0–15.4)
F2	rs1799963	1.28 (0.77–2.14)	0.01	0.4 (−0.7–1.7)
PE				
ABO	rs8176719	1.30 (1.10–1.54)	0.62	15.6 (2.7–28.2)
F11	rs2036914	1.23 (1.00–1.52)	0.78	15.5 (−3.7–34.1)
F11	rs2289252	1.27 (1.07–1.50)	0.63	14.3 (1.2–27.3)
FVL	rs6025	1.52 (1.17–1.97)	0.07	3.3 (0.2–6.8)
FGG	rs2066865	1.14 (0.97–1.34)	0.42	5.6 (−3.2–14.8)
F2	rs1799963	1.93 (1.16–3.23)	0.01	1.2 (−0.4–3.0)

[a]Adjusted for age (as time scale), sex, and body mass index.
[b]≥1 risk allele.

Table 5 Population-attributable fraction (PAF) of venous thromboembolism (VTE) for individual single-nucleotide polymorphisms (SNPs) stratified by age group (<70 and ≥ 70 years)

Gene	SNP	HR (95% CI)[a]	Subcohort prevalence[b]	PAF (95% CI)
<70 years				
ABO	rs8176719	1.65 (1.40–1.96)	0.62	28.7 (16.7–34.6)
F11	rs2036914	1.33 (1.09–1.62)	0.78	20.4 (3.9–35.3)
F11	rs2289252	1.26 (1.07–1.48)	0.63	13.9 (0.6–24.6)
FVL	rs6025	2.31 (1.88–2.85)	0.07	8.1 (4.2–13.1)
FGG	rs2066865	1.30 (1.12–1.51)	0.42	11.3 (3.0–20.5)
F2	rs1799963	1.51 (0.90–2.52)	0.01	0.7 (−0.7–2.0)
≥70 years				
ABO	rs8176719	1.19 (1.03–1.38)	0.61	10.6 (2.6–23.1)
F11	rs2036914	1.13 (0.95–1.35)	0.79	9.5 (−9.1–23.5)
F11	rs2289252	1.23 (1.06–1.43)	0.63	12.8 (-0.7–23.6)
FVL	rs6025	2.30 (1.88–2.81)	0.07	7.9 (4.7–11.2)
FGG	rs2066865	1.07 (0.93–1.23)	0.41	2.9 (−2.7–11.3)
F2	rs1799963	1.56 (0.94–2.60)	0.01	0.7 (−0.6–2.0)

[a]Adjusted for age (as time scale), sex, and body mass index.
[b]≥1 risk allele.

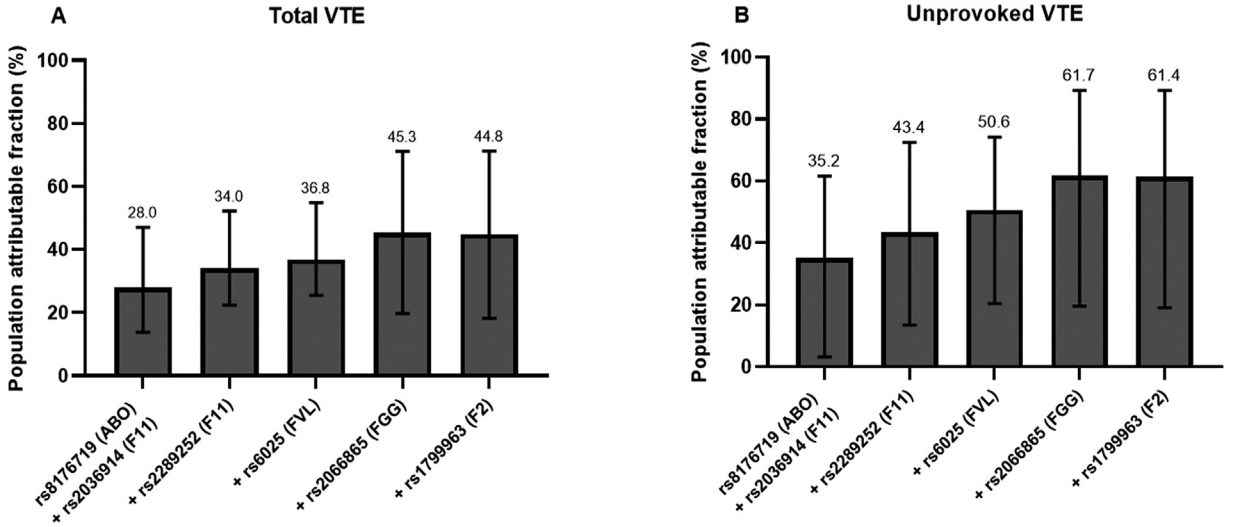


Fig. 1 Cumulative population-attributable fraction (PAF) with 95% confidence intervals of total (**A**) and unprovoked (**B**) venous thromboembolism (VTE) based on increasing number of single-nucleotide polymorphisms (SNPs). SNPs were added in ranked order of the individual PAF estimates (►**Table 4**).

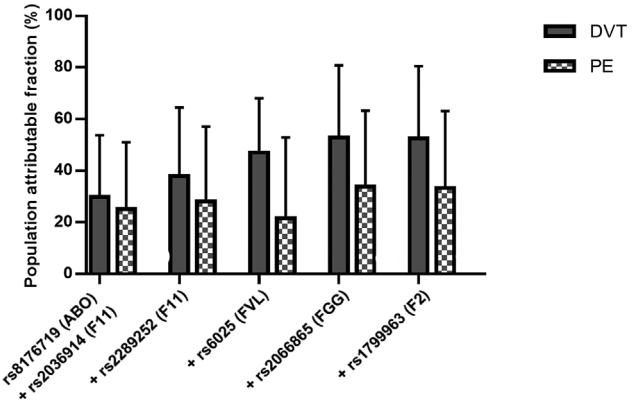


Fig. 2 Cumulative population-attributable fraction (PAF) of deep vein thrombosis (DVT) and pulmonary embolism (PE) based on increasing number of single-nucleotide polymorphisms (SNPs).

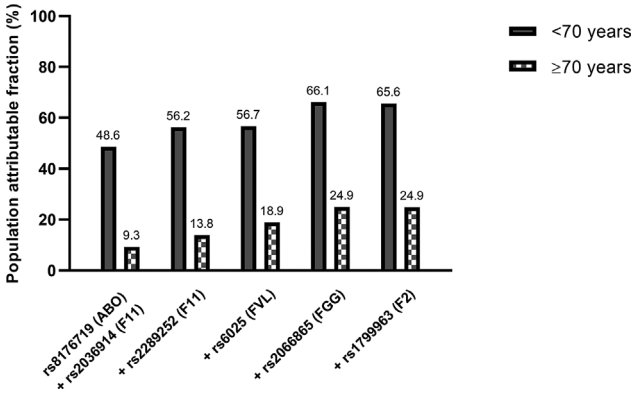


Fig. 3 Cumulative population-attributable fraction (PAF) of venous thromboembolism based on increasing number of single-nucleotide polymorphisms stratified by age (<70 and ≥70 years).

population. A larger proportion of the VTEs could be attributed to genotypes in the young (66%) than in the elderly (25%), and the cumulative PAF was also higher in DVT (53%) than in PE (34%).

When the SNPs associated with VTE risk were added in the cumulative model, the PAF estimate increased until five SNPs were added. The SNPs that were included were rs8176719 (ABO), rs2036914 (F11), rs2289252 (F11), rs6025 (FVL), and rs2066865 (FGG), and the summary PAF for this model suggested that 45% of the VTE events in the population could be attributed to these variants. This is in accordance with a previous study reporting a joint PAF of 35% for three of these SNPs (i.e., rs1799963, rs6025, and rs8176719).[13] Interestingly, four of the SNPs were also included in the 5-SNP genetic risk score developed by de Haan and colleagues, which was found to have similar discriminatory accuracy as a risk score composed of 31 SNPs.[10]

In accordance with previous studies, we found that the non-O blood type (rs8176719) had the largest impact on VTE in the population, accounting for 19% of all events.[13,24,27] The relatively large contribution from this variant is explained by a weak-to-moderate effect size combined with a relatively high prevalence. Our PAF estimate is in accordance with reports from a population-based cohort which reported a PAF of 20% for non-O blood type,[24] while the estimates derived from case–control studies tended to be higher (30–40%).[13,27] Further, we found that the two F11 SNPs contributed significantly to VTE in the population, with PAFs of 13 to 14%. However, our PAF estimates were markedly lower than those previously reported in a case–control study (24–28%).[22] For FVL and the prothrombin mutation G2021A, our PAF estimates were in accordance with previous studies,[13,24,27–29] although considerable variations exist between geographical locations due to differences in prevalence.[30] For instance, in the Netherlands and in southern Sweden, the high prevalence of the FVL mutation yielded PAF estimates of 20 to 50%.[30] In addition, the observed differences in reported PAF estimates could to some extent be explained by differences in study design, as higher estimates are typically

reported in case–control studies. If the distribution of exposure in the control population differs from that of the source population, the true effect may be overestimated, and consequently, the PAF will also be overestimated.

Although we are not aware of previous studies investigating the joint PAF for unprovoked VTE, our findings of a stronger genetic influence is in accordance with studies reporting higher prevalence of thrombophilia among patients with unprovoked VTE.[31] Higher effect sizes in unprovoked compared with total or provoked VTE have been suggested for several prothrombotic genotypes, including the prothrombin G2021A mutation and FVL.[29] The observation that 60% of the unprovoked events can be attributed to these genotypes highlights the need for unraveling novel genetic or environmental risk factors for unprovoked VTE. The characteristics of yet unknown genotypes may be either common variants with very low effect sizes, or extremely rare or private mutations with large effect sizes. In a recent genome-wide/transcriptome-wide association study (GWAS/TWAS) including >30,000 VTE cases and >170,000 controls from 18 studies in the INVENT consortium, 16 novel susceptibility loci for VTE were identified.[9] However, the effect sizes (odds ratios) for these variants were small, ranging from 0.80 to 1.14. Furthermore, the INVENT consortium also performed an exome-wide array analysis based on data from 11 studies to identify novel associations with VTE for low-frequency variants.[32] While associations with previously known loci were confirmed, no new variants were identified, and larger studies with sequencing data were requested.[32] In the other end of the continuum, rare mutations with large effect sizes may be identified in family studies. Importantly, variants with these characteristics will have a small impact on the burden of VTE at the population level.

Using the cumulative model, we found that the PAF of prothrombotic genotypes was higher for DVT than for PE. This difference appeared to be mainly driven by a higher PAF for DVT by the individual SNPs in ABO and FVL. For ABO, previous studies have not reported major differences in the risk of DVT and PE.[16] Accordingly, the HRs for DVT (HR: 1.46) and PE (HR: 1.29) according to ABO status were not statistically different in our study, but the resulting individual PAF estimates were 21.2% for DVT and 15.6% for PE. For FVL, the risk estimates for DVT were significantly higher than for PE, and the individual PAFs were 11.2% in DVT and 3.3% in PE. The higher risk of DVT than of PE in subjects with FVL is well recognized and often referred to as the "FVL paradox."[16] This phenomenon could be explained by the formation of more stable clots less susceptible for embolization in patients with FVL. Indeed, a recent experimental study in mice reported that thrombi in FVL carriers were larger and embolized less compared with wild type.[33]

In the present study, we found that the prothrombotic genotypes exerted a stronger influence on the occurrence of VTE among individuals <70 years. The higher PAF for prothrombotic genotypes in the younger age group was particularly explained by higher HRs of VTE for the SNPs rs8176719 (ABO), rs2303914 (F11), and rs2066865 (FGG). An age effect has previously been reported for the association between family history and the risk of VTE, with the highest effect sizes observed in the younger age groups.[34,35] Further, the proportion of cases with a prothrombotic genotype has been reported to be significantly higher among those aged 20 years or younger (49.3%) compared with those aged 70 years and older (21.9%), suggesting that individuals with a genetic susceptibility experience VTE at a younger age.[31] As aging is associated with an accumulation of acquired and environmental risk factors, the relative contribution of the genetic factors may be diluted. The age effect may also be explained by the phenomenon "attrition of susceptibles" where those highly vulnerable are likely to develop thrombosis early in life, and an apparently resilient elderly population.[15]

The main strengths of our study include the recruitment of participants from a general population cohort with a wide age range, unselected and objectively validated VTEs, and comprehensive information on a large number of prothrombotic genotypes. Our findings are derived from a Caucasian population, which lowers the risk of population stratification, but limits the generalizability of the results to other ethnicities. The PAF is specific for the population it is derived from, and differences in allele frequency between populations have implications for the relevance of the mutation and the occurrence of thrombosis. PAF depends on both the prevalence of the risk factor and its effect size. Importantly, these estimates are only valid under the assumption that the risk factor is causal and are also specific for the population from which they were derived.[26,30] Although PAF is a useful tool to study the impact of genetic factors, its direct dependence on prevalence might lead to overestimation when the prevalence is very high.[11,36] Due to a high prevalence in the cumulative PAF model, the percentages may be overestimated. Finally, the rs8176719 used in this study is not optimal for evaluating VTE risk mediated by the ABO locus as it does not take into account the A2 and O2 blood groups which are associated with a lower risk of VTE compared with A1 and B.[37] However, as the prevalence of A2 and O2 in the population is low (haplotype frequencies <5% and <1%, respectively), this is likely to have a negligible influence on our estimated PAF.

In conclusion, we found that 45% of all VTEs and 62% of the unprovoked VTEs in the population could be attributed to established prothrombotic genotypes, and that this was mainly explained by five SNPs. The proportion of events that could be attributed to genes was higher in the young than in the elderly, and higher in DVT than in PE.

What is known about this topic?

- Venous thromboembolism (VTE) has a strong heritable component.
- Several prothrombotic genotypes have been identified.
- The proportion of VTEs in the population that can be attributed to known prothrombotic genotypes is unclear.

What does this paper add?

- We have estimated the population-attributable fraction (PAF) of prothrombotic genotypes in VTE.
- We show that 45 to 62% of all VTE events in the population can be attributed to five known prothrombotic genotypes.
- A higher proportion of VTEs can be attributed to prothrombotic genotypes in the young than in the elderly.

Author Contributions
Conception and design: L.H.E., J-.B.H., S.K.B., F.R.R. Data collection: J-.B.H., S.K.B., M.E.G., K.H. Draft of manuscript: L.H.E., J-.B.H., S.K.B. Interpretation of results: L.H.E., C.A.L.A., F.R.R., M.E.G., B.M.B., K.H., J-.B.H., S.K.B. Critical revision: L.H.E., C.A.L.A., F.R.R., M.E.G., B.M.B., K.H., J-.B.H., S.K.B.

Funding
K.G. Jebsen Thrombosis Research and Expertise Center (TREC) received an independent grant from Stiftelsen Kristian Gerhard Jebsen in the period 2014–2020.

Conflict of Interest
None declared.

References

1 Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. Br J Haematol 2010;149(06):824–833
2 Crous-Bou M, Harrington LB, Kabrhel C. Environmental and genetic risk factors associated with venous thromboembolism. Semin Thromb Hemost 2016;42(08):808–820
3 Egeberg O. Inherited antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 1965;13:516–530
4 Germain M, Chasman DI, de Haan H, et al; Cardiogenics Consortium. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. Am J Hum Genet 2015;96(04):532–542
5 Trégouët DA, Morange PE. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. Br J Haematol 2018;180(03):335–345
6 Morange PE, Suchon P, Trégouët DA. Genetics of venous thrombosis: update in 2015. Thromb Haemost 2015;114(05):910–919
7 Klarin D, Emdin CA, Natarajan P, Conrad MF, Kathiresan SINVENT Consortium. Genetic analysis of venous thromboembolism in UK Biobank identifies the ZFPM2 locus and implicates obesity as a causal risk factor. Circ Cardiovasc Genet 2017;10(02):e001643
8 Klarin D, Busenkell E, Judy R, et al; INVENT Consortium Veterans Affairs' Million Veteran Program. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. Nat Genet 2019;51(11):1574–1579
9 Lindström S, Wang L, Smith EN, et al; Million Veteran Program CHARGE Hemostasis Working Group. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. Blood 2019;134(19):1645–1657
10 de Haan HG, Bezemer ID, Doggen CJ, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. Blood 2012;120(03):656–663
11 Witte JS, Visscher PM, Wray NR. The contribution of genetic variants to disease depends on the ruler. Nat Rev Genet 2014;15(11):765–776
12 Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88(01):15–19
13 Heit JA, Cunningham JM, Petterson TM, Armasu SM, Rider DN, DE Andrade M. Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism. J Thromb Haemost 2011;9(06):1133–1142
14 Arshad N, Isaksen T, Hansen JB, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol 2017;32(04):299–305
15 Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost 2010;8(10):2105–2112
16 van Langevelde K, Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. Blood 2012;120(05):933–946
17 Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromso study. Int J Epidemiol 2012;41(04):961–967
18 Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995–1997 (HUNT 2): objectives, contents, methods and participation. Nor Epidemiol 2003;13:19–32
19 Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromsø study. J Thromb Haemost 2008;6(11):1851–1857
20 Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5(04):692–699
21 Horvei LD, Braekkan SK, Smith EN, et al. Joint effects of prothrombotic genotypes and body height on the risk of venous thromboembolism: the Tromsø study. J Thromb Haemost 2018;16(01):83–89
22 Li Y, Bezemer ID, Rowland CM, et al. Genetic variants associated with deep vein thrombosis: the F11 locus. J Thromb Haemost 2009;7(11):1802–1808
23 Johnson CY, Tuite A, Morange PE, Tregouet DA, Gagnon F. The factor XII -4C>T variant and risk of common thrombotic disorders: a HuGE review and meta-analysis of evidence from observational studies. Am J Epidemiol 2011;173(02):136–144
24 Sode BF, Allin KH, Dahl M, Gyntelberg F, Nordestgaard BG. Risk of venous thromboembolism and myocardial infarction associated with factor V Leiden and prothrombin mutations and blood type. CMAJ 2013;185(05):E229–E237
25 Zapata-Diomedi B, Barendregt JJ, Veerman JL. Population attributable fraction: names, types and issues with incorrect interpretation of relative risks. Br J Sports Med 2018;52(04):212–213
26 Bhopal RJ. Concepts of Epidemiology. Integrating the Ideas, Theories, Principles, and Methods of Epidemiology. 3rd ed. Oxford: Oxford University Press; 2016
27 Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. J Thromb Haemost 2014;12(10):1593–1600
28 Zöller B, Melander O, Svensson PJ, Engström G. Factor V Leiden paradox in a middle-aged Swedish population: a prospective study. Vasc Med 2018;23(01):52–59
29 Folsom AR, Cushman M, Tsai MY, Heckbert SR, Aleksic N. Prospective study of the G20210A polymorphism in the prothrombin

gene, plasma prothrombin concentration, and incidence of venous thromboembolism. Am J Hematol 2002;71(04):285–290
30 Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost 1999;82(02):610–619
31 Weingarz L, Schwonberg J, Schindewolf M, et al. Prevalence of thrombophilia according to age at the first manifestation of venous thromboembolism: results from the MAISTHRO registry. Br J Haematol 2013;163(05):655–665
32 Lindström S, Brody JA, Turman C, et al; INVENT Consortium. A large-scale exome array analysis of venous thromboembolism. Genet Epidemiol 2019;43(04):449–457
33 Shaya SA, Westrick RJ, Gross PL. Thrombus stability explains the factor V Leiden paradox: a mouse model. Blood Adv 2019;3(21): 3375–3378
34 Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med 2009;169(06):610–615
35 Zöller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation 2011;124(09):1012–1020
36 Rockhill B, Weinberg CR, Newman B. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. Am J Epidemiol 1998;147(09):826–833
37 Goumidi L, Thibord F, Wiggins KL, et al. Association between ABO haplotypes and the risk of venous thrombosis: impact on disease risk estimation. Blood 2021;137(17):2394–2402

Paper III

Received: 20 November 2023 | Revised: 30 January 2024 | Accepted: 31 January 2024

https://doi.org/10.1016/j.rpth.2024.102343

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

Proportion of venous thromboembolism attributed to recognized prothrombotic genotypes in men and women

Carl Arne Løchen Arnesen[1,2] | Line H. Evensen[1] | Kristian Hveem[3,4,5] | Maiken E. Gabrielsen[3] | John-Bjarne Hansen[1,2] | Sigrid K. Brækkan[1,2]

[1]Thrombosis Research Group, Department of Clinical Medicine, UiT–The Arctic University of Norway, Tromsø, Norway

[2]Thrombosis Research Center, Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

[3]HUNT Center for Molecular and Clinical Epidemiology, Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

[4]HUNT Research Center, Department of Public Health and Nursing, Norwegian University of Science and Technology, Levanger, Norway

[5]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

Correspondence
Carl Arne Løchen Arnesen, Thrombosis Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Universitetsvegen 57, Tromsø 9019, Norway.
Email: carl.a.arnesen@uit.no

Handling Editor: Dr Suely Rezende

Abstract

Background: Data on the proportion of venous thromboembolism (VTE) risk attributed to prothrombotic genotypes in men and women are limited.

Objectives: We aimed to estimate the population attributable fraction (PAF) of VTE for recognized, common prothrombotic genotypes in men and women using a population-based case cohort.

Methods: Cases with incident VTE (n = 1493) and a randomly sampled subcohort (n = 13,069) were derived from the Tromsø study (1994-2012) and the Trøndelag Health Study (1995-2008) cohorts. DNA samples were genotyped for 17 single-nucleotide polymorphisms (SNPs) previously associated with VTE. PAFs with 95% bias-corrected CIs (based on 10,000 bootstrap samples) were estimated for SNPs significantly associated with VTE, and a 6-SNP cumulative model was constructed for both sexes.

Results: In women, the individual PAFs for SNPs included in the cumulative model were 16.9% for *ABO* (rs8176719), 17.6% for *F11* (rs2036914), 15.1% for *F11* (rs2289252), 8.7% for *FVL* (rs6025), 6.0% for *FGG* (rs2066865), and 0.2% for *F2* (rs1799963). The cumulative PAF for this 6-SNP model was 37.8%. In men, the individual PAFs for SNPs included in the cumulative model were 21.3% for *ABO*, 12.2% for *F11* (rs2036914), 10.4% for *F11* (rs2289252), 7.5% for *FVL*, 7.8% for *FGG*, and 1.1% for *F2*. This resulted in a cumulative PAF in men of 51.9%.

Conclusion: Our findings in a Norwegian population suggest that 52% and 38% of the VTEs can be attributed to known prothrombotic genotypes in men and women, respectively.

KEYWORDS
epidemiology, risk factors, sex differences, single-nucleotide polymorphism, venous thromboembolism

Essentials

- Sex-specific data on venous thrombosis risk attributed to prothrombotic genotypes are scarce.
- We estimated the cumulative population attributable risk of 6 single-nucleotide polymorphisms in men and women.
- For this 6-single-nucleotide polymorphism model, the cumulative population attributable risk was 51.9% in men and 37.8% in women.
- Prothrombotic genotypes appeared to explain a higher proportion of venous thromboses in men than in women.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a common and complex disease that is the result of both genetic and environmental factors [1]. The risk of VTE in men vs women has been shown to vary according to age, with a higher risk in women than in men among the young (<50 years) and a higher risk in men than in women among the middle-aged (50-75 years) [2,3]. Even though the overall lifetime risk of VTE appears to be similar in men and women [4], the contribution of different risk factors to disease development may vary across both sex and age.

VTE has a strong hereditary component, and family and twin studies have suggested an overall VTE heritability of 45% to 60% [5–9]. Of note, some family studies suggest a stronger genetic component in men than in women [9], whereas others find little [7] or no overall difference [5]. Several single-nucleotide polymorphisms (SNPs) associated with increased VTE risk have been detected [10–14], and genome-wide association studies (GWASs) report that the recognized prothrombotic SNPs contribute 15% to 20% of the VTE heritability [15]. Few studies have investigated the impact of the recently identified SNPs on VTE risk in men and women separately. Moreover, the proportion of the VTEs that can be attributed to these SNPs in men and women in different age groups has not been studied in a general population.

Population attributable fraction (PAF) estimates the fraction of disease that potentially can be prevented if efficient interventions are available [16,17]. From an epidemiological perspective, PAF is a useful tool to quantify disease risk attributable to genetic factors. We have previously shown that a 6-SNP cumulative PAF model explained about 45% of all VTEs in the population [18]. Whether the individual and combined PAFs of known prothrombotic SNPs for VTE are similar in men and women has not been addressed. Additionally, whether genetic risk impacts men and women differently in certain age groups has not been extensively studied. Therefore, this study aimed to estimate (i) the individual and cumulative PAF of established prothrombotic SNPs in men and women and (ii) the cumulative PAF in men and women across age groups in a population-based case cohort.

2 | METHODS

2.1 | Study population

The population under study was derived from the fourth survey of the Tromsø study (Tromsø 4) and the second survey of the Trøndelag Health Study (HUNT). Both studies are population-based cohort studies of residents in the Tromsø municipality and Nord-Trøndelag County, respectively. To Tromsø 4 (1994/1995), all residents aged at least 25 years were invited, and 77% (27,158) participated. To the second survey of HUNT (1995-1997), all residents aged at least 20 years were invited, and 71% (66,140) participated. A thorough description of the Tromsø [19] and HUNT [20] studies can be found in their cohort profile papers.

Follow-up of participants started from the inclusion date in the respective cohort surveys and lasted until the date of incident VTE, migration, death, or end of follow-up (December 31, 2012, in Tromsø and December 31, 2008, in HUNT), whichever occurred first. The procedures for identification of all VTEs in the Tromsø study [21] and the HUNT Study [22] have been extensively presented elsewhere and will be briefly summarized here. For the Tromsø study, information on VTE events was obtained by searching the radiology procedure registry, the autopsy registry, and the hospital discharge diagnosis registry at the University Hospital of North Norway. The medical documents of each patient were carefully examined. The adjudication criteria for VTE were symptoms and signs of pulmonary embolism or deep vein thrombosis, followed by objective verification by radiological imaging and initiation of anticoagulant treatment (unless treatment contraindications were present). In the HUNT Study, identification of VTE events was obtained by searching the radiology procedure registry and the discharge diagnosis registry at the 2 local hospitals, Namsos and Levanger, as well as the discharge diagnosis registry at St. Olavs Hospital in Trondheim, the tertiary care center of the region. Two doctors examined the medical records, and all radiologically verified VTE events among the participants were recorded.

A case cohort was created based on all cases with a first-lifetime VTE (n = 1493) and a subcohort (n = 13,072) randomly sampled from the source cohorts (Tromsø and HUNT). Participants in the source cohorts with a known VTE event before attending the baseline survey were excluded before the creation of the case cohort. Participants not registered as residents of Tromsø or Nord-Trøndelag at study inclusion (n = 3) were excluded. Ultimately, the case cohort consisted of 14,562 participants (1493 VTE cases and 13,069 subcohort participants). The composition of the case cohort is displayed in Figure 1. When sampling the subcohort, every person in the source cohort (including cases) has the same probability of being sampled. Therefore, 217 of the VTE cases were by chance also sampled to the subcohort. The Regional Committee of Medical Health Research Ethics approved the study, and all study participants gave their informed written consent to participate.

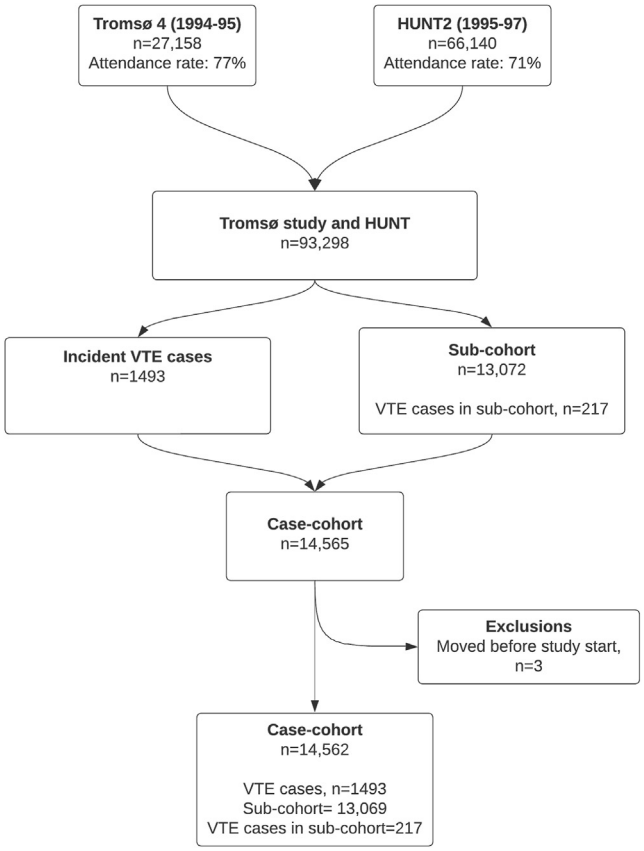


FIGURE 1 Overview of the case cohort study composition. HUNT, Trøndelag Health Study; HUNT2, second survey of the Trøndelag Health Study; Tromsø 4, fourth survey of the Tromsø Study; VTE, venous thromboembolism.

2.2 | Baseline measurements

Baseline information was collected by physical examinations, blood samples, and self-administered questionnaires in both studies. Information on arterial cardiovascular disease (stroke, myocardial infarction, and angina) and diabetes was self-reported. Measurement of weight and body height was conducted with participants wearing no shoes and light clothing, and body mass index (BMI) was calculated.

2.3 | SNP selections and genotyping

Genotyping was performed for 17 SNPs with recognized association with VTE risk. The TaqMan (Thermo Fisher) and Sequenom platforms (Sequenom) were used for genotyping in the Tromsø study, as previously documented [10], while the Illumina HumanCore Exome array was used for genotyping in HUNT.

Participants were categorized as carriers (≥1 risk allele), or noncarriers (0 risk alleles), and no distinction was made between hetero- and homozygous carriers in the PAF and hazard ratio (HR) analyses. For the SNPs rs2036914 (*F11*), rs1801020 (*F12*), rs1039084 (*STXBP5*), rs1884841 (*TC2N*), rs1613662 (*GP6*), and rs4524 (*F5*), the major alleles were labeled as the risk alleles [11–13,23]. For the rs8176719 SNP (in *ABO*), the G allele marks non-O blood type (risk group), while those who were homozygous carriers for deletion at this site were classified as blood type O and served as the reference group [23].

2.4 | Statistical analysis

Stata version 16 (Stata Corp) was used to run the statistical analyses. The person-time of follow-up was accumulated from the date of inclusion for each participant until the date of first-time VTE, migration, death, or the end of follow-up. Follow-up ended on December 31, 2012, in Tromsø and on December 31, 2008, in HUNT. All analyses were run distinctly for women and men. For each SNP, sex-specific HRs for VTE with 95% CIs were estimated using Cox regression models with noncarriers (0 risk alleles) serving as reference category. Age served as a time scale. The entry time was the age at inclusion, and the exit time was the age at VTE/censoring. The HR model was adjusted for BMI. Schoenfeld residuals were used to evaluate the proportional hazards assumption, which was not violated.

PAF was calculated for each SNP using the formula $\frac{p(HR-1)}{p(HR-1)+1}$, where *HR* is the VTE risk in carriers vs noncarriers of the risk allele, and *p* is the prevalence of carriers in the population [16]. We applied a cumulative PAF model previously created by Evensen et al. [18]. The model was constructed by adding SNPs one-by-one in order based on the highest individual PAF estimates, beginning with the 2 SNPs with the highest estimates in the total population. Despite a low PAF, prothrombin (*F2*) was added to the model due to its considerable HR and because it is a well-recognized risk factor for VTE. The SNPs included in this cumulative PAF model were *ABO* (rs8176719), *F11* (rs2036914), *F11* (rs2289252), *FVL* (rs6025), *FGG* (rs2066865), and *F2* (rs1799963). The model was applied to men and women separately. The calculation of 95% bias-corrected CIs for the PAF estimates was based on 10,000 bootstrap samples. We also calculated the cumulative PAF of the 6-SNP model according to separate age groups (≤50, 50-75, and >75 years) in men and women. We omitted individuals with missing information on SNPs included in the cumulative PAF model (women, n = 28; men, n = 87) and BMI (women, n = 66; men, n = 25) from these analyses (to preserve identical samples in each analysis).

3 | RESULTS

Descriptive information on VTE cases and the subcohort according to sex are displayed in Table 1. Mean age, systolic blood pressure, BMI, diabetes, and the proportion of arterial cardiovascular diseases were higher among the VTE cases compared with the subcohort in both sexes.

Sex-specific allele frequencies and distribution of risk alleles for all prothrombotic SNPs in the cases and the subcohort are shown in Table 2. In the subcohort, the allele frequencies were essentially

TABLE 1 Baseline characteristics of venous thromboembolism cases and the subcohort.

	VTE cases (*n* = 1493)		Subcohort (*n* = 13,069)	
	Women (*n* = 790)	Men (*n* = 703)	Women (*n* = 6909)	Men (*n* = 6160)
Age (y), mean ± SD	62 ± 15	60 ± 13	51 ± 17	50 ± 16
BMI (kg/m^2), mean ± SD	27.9 ± 5.0	26.9 ± 3.6	26.2 ± 4.6	26.3 ± 3.5
Systolic blood pressure (mm Hg), mean ± SD	145.9 ± 25.0	143.8 ± 20.8	136.4 ± 24.2	140.1 ± 18.6
Arterial cardiovascular disease,[a] % (*n*)	11.8 (93)	16.2 (114)	6.1 (420)	10.1 (619)
Diabetes, % (*n*)	4.1 (32)	4.6 (32)	3.1 (217)	3.1 (193)
History of cancer, % (*n*)	7.2 (57)	5.5 (39)	4.1 (280)	3.1 (193)

BMI, body mass index; VTE, venous thromboembolism.
[a]Myocardial infarction, stroke, and angina.

similar in men and women and comparable to those reported in other populations of European ancestry [24].

Table 3 contains the sex-specific HRs and PAF estimates with 95% CIs of VTE for all 17 individual SNPs. As displayed in Table 3, the HRs and PAFs of the individual SNPs diverged somewhat between the sexes. The most noticeable differences in PAFs were found for rs1884841 (*TC2N*: 11.6%; 95% CI, −1.3% to 24.4% in women vs 2.1%; 95% CI, −11.8% to 15.9% in men), rs2036914 (*F11*: 17.6%; 95% CI, 0.4%-34.1% for women vs 12.2%; 95% CI, −5.5% to 29.2% for men), rs8176719 (*ABO*: 16.9%; 95% CI, 5.8%-28.0% for women vs 21.3%; 95% CI, 9.6%-32.5% for men), and rs2289252 (*F11*: 15.1%; 95% CI, 3.4%-26.7% for women vs 10.4%; 95% CI, −2.0% to 22.4% for men).

Figure 2 shows the results of the previously established 6-SNP cumulative PAF model for women (Figure 2A) and men (Figure 2B) separately. In total, 51.9% of the VTE cases in the male population could be explained by these 6 SNPs, while the corresponding estimate in the female population was only 37.8%. The cumulative PAFs for the 6-SNP model according to age groups in men and women are shown in Figure 3. In those <50 years, the cumulative PAF was 46.6% and 53.7% in women and men, respectively, while the corresponding PAF in those aged 50 to 75 years was 54.5% (women) and 73.0% (men). In people >75 years, the cumulative PAF of the 6 SNPs was 12.9% in women and 14.1% in men.

4 | DISCUSSION

In the present study, we investigated the individual risk of VTE contributed by 17 known prothrombotic genotypes in men and women and estimated the total and age-specific cumulative PAF for the combination of 6 SNPs (*ABO*, *F11* [rs2289252], *F11* [rs2036914], *FVL*, *FGG*, and *F2*). Even though the frequencies of the 17 SNPs did not differ between men and women, the relative risk estimates and individual PAFs differed slightly for some of the SNPs. Furthermore, the fraction of VTEs that could be ascribed to the 6 prothrombotic SNPs was 38% in women and 52% in men. Analyses stratified into young, middle-aged, and elderly individuals showed cumulative PAFs of 54%, 73%, and 14% in men, respectively, while the corresponding PAFs in women were 47%, 54%, and 13%, respectively. Thus, particularly among the middle-aged, prothrombotic genotypes appeared to explain a higher proportion of the VTE events in men than in women.

Few studies have reported on the association between all 17 SNPs and the risk of VTE in men and women separately. Neither of these SNPs is linked to sex chromosomes, and as expected, the allele frequencies of the various SNPs were similar in men and women in our subcohort. Moreover, the allele frequencies in our study corresponded well with those reported in other Caucasian populations [25–27]. Using the Multiple environmental and genetic assessment of risk factors for venous thrombosis (MEGA) case-control study, Roach et al. [28] investigated the effect of *FVL*, prothrombin mutation, and non-O blood group on the risk of VTE in men and women separately. They reported similar odds ratios (ORs) and PAFs for both sexes, with individual PAFs in men and women of 10% and 8% for *FVL*, 4% and 3% for prothrombin, and 39% and 35% for non-O blood group, respectively. For prothrombin and the non-O blood group, the ORs and PAF estimates in MEGA were considerably higher than in our study. This may depend to some extent on the case-control design and the younger age distribution (and thereby lower baseline risk of VTE) of the MEGA participants. Of note, our risk estimates for *FVL*, *F11*, *FGG*, and *ABO* corresponded well with those reported in a GWAS meta-analysis of 18 studies [15]. We found that rs1884841 in *TC2N* was associated with increased VTE risk in women but not in men, resulting in PAF estimates of 11.6% in women and 2.1% in men. Previous studies on *TC2N* and VTE have shown somewhat diverging results. The study that first identified *TC2N* as a potential risk factor for VTE reported ORs ranging from 1.08 to 1.30 in 3 European case-control studies [11]. A later meta-analysis of GWAS data from 18 studies found a weak association with an OR of 1.05 [15]. Neither of these studies reported risk estimates for men and women separately. In contrast with our findings, 2 studies restricted to women [27,29] reported no association between *TC2N* and VTE (OR, 1.02). Thus, even though our results suggest that *TC2N* could serve as a substantial attributable genetic risk factor in women, we cannot rule out the possibility of a chance finding.

To our knowledge, no study has investigated the cumulative PAF of prothrombotic genotypes in men and women separately. In a

TABLE 2 Sex-specific allele frequency and distribution of risk alleles in venous thromboembolism cases and the subcohort in descending order based on allele frequency in the subcohort.

		VTE cases (*n* = 1493)						Subcohort (*n* = 13,069)					
		Women (*n* = 790)			Men (*n* = 703)			Women (*n* = 6909)			Men (*n* = 6160)		
Gene	SNP	AF (%)	1 risk allele, % (*n*)	2 risk alleles, % (*n*)	AF (%)	1 risk allele, % (*n*)	2 risk alleles, % (*n*)	AF (%)	1 risk allele, % (*n*)	2 risk alleles, % (*n*)	AF (%)	1 risk allele, % (*n*)	2 risk alleles, % (*n*)
GP6	rs1613662	85.0	24.2 (191)	72.9 (576)	87.1	22.1 (155)	76.1 (534)	82.7	29.0 (2005)	68.2 (4708)	82.5	28.3 (1744)	68.4 (4209)
F12	rs1801020	76.5	35.1 (228)	58.9 (383)	76.1	34.6 (203)	58.8 (345)	74.6	37.2 (2517)	56.0 (3788)	74.2	38.9 (2348)	54.7 (3304)
F5	rs4524	75.8	36.0 (284)	57.9 (457)	77.6	37.5 (263)	58.8 (413)	72.8	39.2 (2706)	53.2 (3677)	72.9	39.3 (2416)	53.2 (3277)
F11	rs2036914	58.1	51.1 (404)	32.5 (257)	56.4	47.9 (335)	32.4 (227)	53.3	50.4 (3479)	28.1 (1940)	52.8	49.9 (3054)	27.9 (1706)
STXBP5	rs1039084	53.9	48.4 (382)	29.8 (235)	53.6	47.9 (336)	29.6 (208)	51.3	50.4 (3482)	26.1 (1800)	51.7	50.4 (3100)	26.5 (1631)
TC2N	rs1884841	45.4	53.6 (422)	18.6 (146)	43.5	47.4 (333)	19.8 (139)	43.2	48.1 (3319)	19.2 (1323)	42.9	48.4 (2980)	18.6 (1148)
KNG1	rs710446	43.2	48.2 (381)	19.1 (151)	40.8	44.7 (314)	18.5 (130)	41.5	48.9 (3379)	17.0 (1176)	41.0	47.9 (2947)	17.0 (1048)
F11	rs2289252	45.3	48.4 (382)	21.1 (167)	41.3	49.2 (345)	16.7 (117)	39.3	47.5 (3275)	15.6 (1077)	39.0	47.3 (2913)	15.3 (944)
ABO	rs8176719	42.7	50.6 (400)	17.3 (137)	43.6	52.0 (364)	17.6 (123)	38.3	45.9 (3166)	15.3 (1056)	38.4	46.7 (2861)	15.1 (922)
VWF	rs1063857	37.8	49.8 (377)	13.0 (98)	37.8	46.6 (318)	14.5 (99)	38.3	46.4 (2878)	15.0 (932)	38.0	46.8 (2611)	14.6 (812)
F13	rs5985	29.2	39.4 (253)	9.5 (61)	28.3	41.8 (243)	7.4 (43)	27.2	40.0 (2692)	7.2 (484)	26.1	38.2 (2291)	7.1 (423)
FGG	rs2066865	26.6	35.6 (281)	8.9 (70)	28.0	39.5 (278)	8.3 (58)	23.6	36.1 (2845)	5.6 (386)	24.3	36.6 (2255)	6.0 (370)
SERP	rs2227589	10.4	18.5 (146)	9 (1.1)	9.0	15.8 (111)	1.1 (8)	8.8	15.8 (1091)	0.9 (59)	8.7	15.9 (978)	0.8 (48)
C4BPB	rs3813948	7.8	14.6 (115)	0.5 (4)	7.0	12.8 (90)	0.6 (4)	7.7	14.3 (986)	0.6 (39)	7.6	14.0 (862)	0.6 (39)
FVL	rs6025	7.9	15.0 (118)	0.4 (3)	7.6	13.7 (96)	0.7 (5)	3.3	6.3 (434)	0.1 (10)	3.5	6.8 (420)	0.1 (5)
F2	rs3136520	3.0	5.8 (45)	0.1 (1)	3.3	6.0 (42)	0.3 (2)	3.1	6.0 (413)	0.1 (7)	3.0	5.7 (350)	0.2 (9)
F2	rs1799963	0.8	1.5 (12)	-	1.4	2.7 (19)	-	0.6	1.2 (85)	-	0.7	1.4 (88)	-

AF, allele frequency; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism.

TABLE 3 Hazard ratio and population attributable fraction with 95% CIs for venous thromboembolism by individual single-nucleotide polymorphisms in men and women in alphabetical order.

		Women			Men		
Gene	SNP	Subcohort prevalence[a]	HR (95% CI)[b]	PAF (95% CI)	Subcohort prevalence[a]	HR (95% CI)[b]	PAF (95% CI)
ABO	rs8176719	0.61	1.33 (1.15 to 1.55)	16.9 (5.8 to 28.0)	0.62	1.44 (1.23 to 1.69)	21.3 (9.6 to 32.5)
C4BPB	rs3813948	0.15	1.01 (0.83 to 1.23)	0.2 (−3.5 to 4.2)	0.15	0.93 (0.75 to 1.16)	−1.0 (−4.8 to 2.9)
FGG	rs2066865	0.42	1.15 (1.00 to 1.33)	6.0 (−1.8 to 14.2)	0.43	1.20 (1.03 to 1.39)	7.8 (−0.5 to 16.0)
FVL	rs6025	0.06	2.48 (2.04 to 3.00)	8.7 (5.4 to 12.3)	0.07	2.17 (1.76 to 2.69)	7.5 (4.0 to 11.2)
F2	rs1799963	0.01	1.17 (0.65 to 2.13)	0.2 (−0.8 to 1.5)	0.01	1.79 (1.13 to 2.81)	1.1 (−0.3 to 2.9)
F2	rs3136520	0.06	0.95 (0.70 to 1.28)	−0.3 (−2.5 to 2.1)	0.06	1.16 (0.85 to 1.57)	0.9 (−1.6 to 3.7)
F5	rs4524	0.92	1.27 (0.95 to 1.70)	20.0 (−10.9 to 47.3)	0.92	1.97 (1.33 to 2.92)	47.3 (19.0 to 72.1)
F11	rs2036914	0.79	1.27 (1.05 to 1.54)	17.6 (0.4 to 34.1)	0.78	1.18 (0.98 to 1.42)	12.2 (−5.5 to 29.2)
F11	rs2289252	0.63	1.28 (1.10 to 1.49)	15.1 (3.4 to 26.7)	0.63	1.19 (1.01 to 1.39)	10.4 (−2.0 to 22.4)
F12	rs1801020	0.93	1.04 (0.75 to 1.44)	3.6 (−38.3 to 38.3)	0.94	0.89 (0.64 to 1.23)	−11.1 (−57.8 to 29.9)
F13	rs5985	0.47	1.07 (0.92 to 1.25)	3.3 (−6.2 to 2.1)	0.45	1.15 (0.97 to 1.35)	6.1 (−3.6 to 15.6)
GP6	rs1613662	0.97	0.9 (0.60 to 1.37)	−10.3 (−74.2 to 44.6)	0.97	1.62 (0.94 to 2.80)	37.5 (−10.2 to 76.4)
KNG1	rs710446	0.66	1.07 (0.92 to 1.24)	4.2 (−8.1 to 16.7)	0.65	0.97 (0.83 to 1.14)	−1.7 (−15.1 to 11.2)
SERP	rs2227589	0.17	1.20 (1.01 to 1.43)	3.2 (−0.9 to 7.7)	0.17	1.00 (0.80 to 1.20)	−0.2 (−4.4 to 4.1)
STXBP5	rs1039084	0.76	1.15 (0.97 to 1.37)	0.1 (−5.3 to 27.0)	0.77	1.03 (0.86 to 1.22)	1.9 (−15.9 to 18.8)
TC2N	rs1884841	0.67	1.20 (1.02 to 1.40)	11.6 (−1.3 to 24.4)	0.67	1.03 (0.88 to 1.20)	2.1 (−11.8 to 15.9)
VWF	rs1063857	0.61	1.05 (0.91 to 1.22)	2.7 (−7.5 to 13.6)	0.61	1.01 (0.87 to 1.18)	0.7 (−10.6 to 12.0)

HR, hazard ratio; PAF, population attributable fraction; SNP, single-nucleotide polymorphism.
[a]Great than or equal to the risk allele.
[b]Adjusted for age (as time scale) and body mass index.

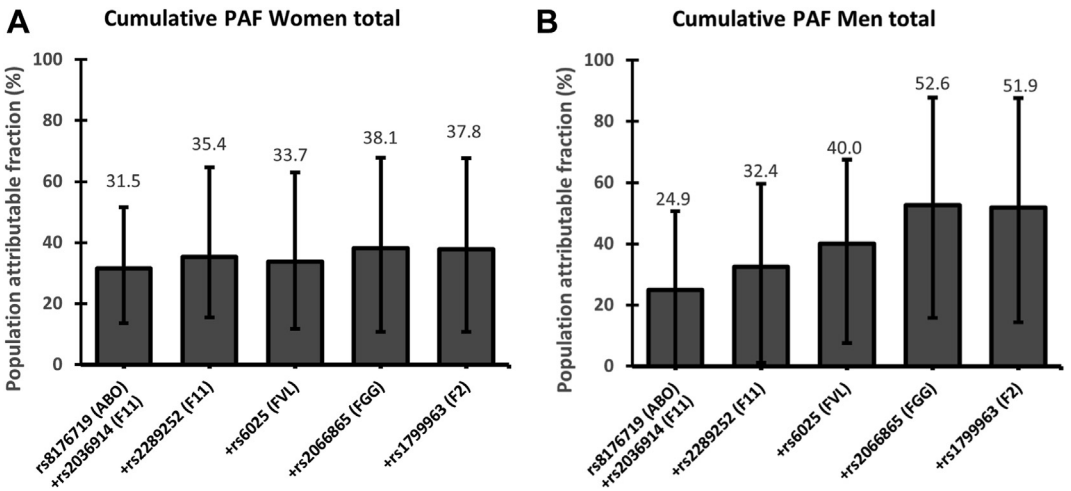


FIGURE 2 Cumulative population attributable fraction (PAF) of venous thromboembolism by increasing number of single-nucleotide polymorphisms (SNPs) in (A) women and (B) men. The following SNPs were included: rs8176719 (*ABO*), rs2036914 (*F11*), rs2289252 (*F11*), rs6025 (*FVL*), rs2066865 (*FGG*), and rs1799963 (*F2*). SNPs were added in order of the individual PAF estimates (Table 3).

case-control study, a joint PAF of 40% was reported for the SNPs in *F2* (rs1799963), *F5* (rs6025), *ABO* (rs2519093), and *ABO* (rs8176719) [26]. However, no sex-specific analyses were presented, and several of the SNPs included in our study were not investigated in their study [26]. We have previously shown that the model containing *ABO*, *F11*, *F11*, *FGG*, *FVL*, and *F2* yielded a cumulative PAF of 45% in the total

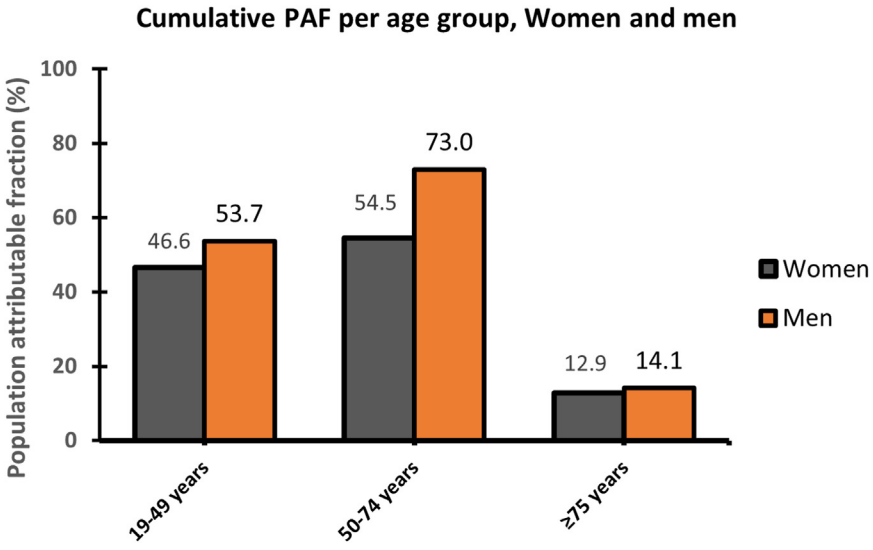


FIGURE 3 Cumulative population attributable fraction (PAF) of prothrombotic single-nucleotide polymorphisms (SNPs) stratified by age (<50, 50-74, and ≤75) for women and men. The following SNPs were included: rs8176719 (*ABO*), rs2036914 (*F11*), rs2289252 (*F11*), rs6025 (*FVL*), rs2066865 (*FGG*), and rs1799963 (*F2*). SNPs were added in order of the individual PAF estimates (Table 3).

population. However, our sex-specific analyses revealed that this model explained a larger proportion (52%) of the VTEs in men than in women (38%).

We found that the portion of VTE events attributable to prothrombotic genotypes varied in men and women of different ages. Few previous studies have investigated sex-specific genetic VTE risk in different age groups. In a cross-sectional study of patients aged >40 years with first-time VTE, Weingarz et al. [30] reported a higher prevalence of thrombophilia in men than in women. Furthermore, Zöller et al. [5] reported slightly higher standardized incidence ratios in men than in women in a nationwide study of siblings aged 20 to 60 years. Of note, the sex differences observed in these studies did not reach statistical significance. In a study of VTE cases and controls aged 18 to 70 years, Roach et al. [31] hypothesized that the observed higher VTE risk in men compared with women without reproductive risk factors could be explained by a genetic risk difference. However, further study of *FVL*, prothrombin, and *ABO*-blood group yielded only marginally higher risk estimates in men than in women in the same population [28]. In our study, there was a moderate difference in the cumulative PAF in individuals aged <50 years (women, 46.6%; men, 53.7%). In this age range, female reproductive risk factors such as pregnancy and oral contraceptives [4,8,28,32] are well-known contributors to VTE risk, and the impact of these strong risk factors may explain why a lower proportion of all VTEs were attributed to genetics in women. Among the middle-aged (50-75 years), the cumulative PAF of prothrombotic genotypes was substantially higher in men than in women in our study (women, 54.5%; men, 73.0%). Considering that the prevalence of reproductive risk factors in the middle-aged is low [33] and that the use of postmenopausal hormonal therapy has declined substantially in the Norwegian population in the last decades [34], it is unlikely that the PAF disparity in this age group is due to reproductive risk factors. A possible explanation could be that women who are genetically susceptible to VTE are affected at a younger age than men with a similar genetic profile due to the additive influence of reproductive risk factors. In addition, genetically susceptible men could be more vulnerable in middle age due to an additive effect from risk factors such as body height [35,36] and obesity [37]. This hypothesis is supported by the "catch-up" effect observed in men within this age range when modeling the cumulative lifetime risk in men and women separately [4]. Finally, the substantially lower PAF of prothrombotic genotypes observed in the elderly (women, 12.9%; men, 14.1%) could be explained by further depletion of susceptibles in both sexes, as well as the higher prevalence of other major VTE risk factors in this age group, such as cancer, surgery, and immobility [8]. This age pattern has previously been reported in both family history and genotype studies [5,18,30], further supporting the idea that people with a prothrombotic genotype usually experience VTE earlier in life, regardless of sex.

Our study used PAF to quantify the proportion of VTEs that could be attributed to known prothrombotic risk factors. The PAF estimate is usually larger than other genetic measures, like heritability [38], which quantifies the effects on the variability of risk at the population level. Although PAF and heritability measure different aspects of genetic contributions to disease risk, the 2 measurements are related [17]. While PAF is a useful tool to analyze the influence of genetic factors, it can be overestimated when the risk factor prevalence is very high due to its direct dependence on prevalence [38,39]. The complete, cumulative PAF models used in our study had a high prevalence, and consequently, the percentages might be somewhat overestimated. However, since the prevalence of the SNPs was similar in men and women, our PAF estimates would still allow for comparison between the sexes.

The main strengths of this study are its prospective design, high participation rate, large number of genotyped participants, and long-term follow-up in both the Tromsø and HUNT studies. Moreover, VTE events were objectively confirmed and systematically validated, and the genotyping had few missing values for most SNPs. The study cohort is a homogenous Caucasian population, which limits the likelihood of confounding by ethnicity but also limits its generalizability beyond this

group. Due to the overlap between the present sample and the sample in which the associations were estimated, our results could be susceptible to overestimation of the genetic association, more commonly known as the winner's curse [40]. To avoid this, we ensured that the SNPs selected for the cumulative PAF models corresponded well with previous observations from the literature [23,26,27,29] and refrained from selecting SNPs based solely on the HRs in our own sample. The statistical power for some subgroup analyses resulting in wide CIs for some of the risk estimates, especially affecting the bootstrap estimates for PAF, implies that these results should be interpreted with caution. We cannot rule out the possibility that some participants included in the subcohort could have had a previous VTE. Nevertheless, the prevalence of (misclassified) previous VTE is expected to be low, and if present, this would likely have a negligible impact on the risk estimates. Additionally, we did not run any subgroup analysis on the type of VTE, which perhaps could have revealed whether some SNPs are more relevant for specific types of VTE.

In conclusion, our findings in a Norwegian population suggest that 52% and 38% of the VTEs can be attributed to known, common prothrombotic genotypes in men and women, respectively. The proportion of VTE events that could be attributed to genotypes varied across age groups in both sexes and was particularly high among middle-aged men. In the elderly, the PAF of prothrombotic genotypes was similar in men and women.

ACKNOWLEDGMENTS

The Trøndelag Health Study is a collaboration between the Trøndelag Health Study Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

FUNDING

The K.G. Jebsen Thrombosis Research and Expertise Center received an independent grant from Stiftelsen Kristian Gerhard Jebsen from 2014 to 2020.

ETHICS STATEMENT

The Regional Committee of Medical Health Research Ethics approved the study, and all study participants gave their informed written consent to participate.

AUTHOR CONTRIBUTIONS

Conception and design: J.-B.H., S.K.B., L.H.E.. Data collection: J.-B.H., S.K.B., K.H., M.E.G.. Data analyses: C.A.L.A., L.H.E.. Interpretation of results: C.A.L.A., L.H.E., J.-B.H., S.K.B., K.H., M.E.G.. Drafting of manuscript: C.A.L.A.. Critical revision of manuscript: J.-B.H., S.K.B., L.H.E., K.H., M.E.G.. Approval of final version: all authors.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

REFERENCES

[1] Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353:1167–73.
[2] Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. 2004;117:19–25.
[3] Arshad N, Isaksen T, Hansen JB, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. 2017;32:299–305.
[4] Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. *Eur J Epidemiol*. 2022;37:195–203.
[5] Zöller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. *Circulation*. 2011;124:1012–20.
[6] Zöller B, Ohlsson H, Sundquist J, Sundquist K. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. *Thromb Haemost*. 2013;109:458–63.
[7] Zöller B, Ohlsson H, Sundquist J, Sundquist K. A sibling based design to quantify genetic and shared environmental effects of venous thromboembolism in Sweden. *Thromb Res*. 2017;149:82–7.
[8] Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12:464–74.
[9] Larsen TB, Sørensen HT, Skytthe A, Johnsen SP, Vaupel JW, Christensen K. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. *Epidemiology*. 2003;14:328–32.
[10] Horvei LD, Braekkan SK, Smith EN, Solomon T, Hindberg K, Frazer KA, et al. Joint effects of prothrombotic genotypes and body height on the risk of venous thromboembolism: the Tromsø study. *J Thromb Haemost*. 2018;16:83–9.
[11] Morange PE, Saut N, Antoni G, Emmerich J, Trégouët DA. Impact on venous thrombosis risk of newly discovered gene variants associated with FVIII and VWF plasma levels. *J Thromb Haemost*. 2011;9:229–31.
[12] Morange PE, Tregouet DA. Lessons from genome-wide association studies in venous thrombosis. *J Thromb Haemost*. 2011;9(Suppl 1):258–64.
[13] Rinde LB, Morelli VM, Småbrekke B, Mathiesen EB, Løchen ML, Njølstad I, et al. Effect of prothrombotic genotypes on the risk of venous thromboembolism in patients with and without ischemic stroke. The Tromsø study. *J Thromb Haemost*. 2019;17:749–58.
[14] Roach RE, Lijfering WM, Tait RC, Baglin T, Kyrle PA, Cannegieter SC, et al. Sex difference in the risk of recurrent venous thrombosis: a detailed analysis in four European cohorts. *J Thromb Haemost*. 2015;13:1815–22.
[15] Lindström S, Wang L, Smith EN, Gordon W, Van Hylckama Vlieg A, De Andrade M, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood*. 2019;134:1645–57.
[16] Zapata-Diomedi B, Barendregt JJ, Veerman JL. Population attributable fraction: names, types and issues with incorrect interpretation of relative risks. *Br J Sports Med*. 2018;52:212–3.
[17] Wang T, Hosgood HD, Lan Q, Xue X. The relationship between population attributable fraction and heritability in genetic studies. *Front Genet*. 2018;9:352. https://doi.org/10.3389/fgene.2018.00352
[18] Evensen LH, Arnesen CAL, Rosendaal FR, Gabrielsen ME, Brumpton BM, Hveem K, et al. The risk of venous thromboembolism attributed to established prothrombotic genotypes. *Thromb Haemost*. 2022;122:1221–30.

[19] Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromso Study. *Int J Epidemiol*. 2012;41:961–7.

[20] Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): objectives, contents, methods and participation. *Nor Epidemiol*. 2003;13:19–32.

[21] Borch KH, Nyegaard C, Hansen JB, Mathiesen EB, Njølstad I, Wilsgaard T, et al. Joint effects of obesity and body height on the risk of venous thromboembolism: the Tromsø study. *Arterioscler Thromb Vasc Biol*. 2011;31:1439–44.

[22] Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5:692–9.

[23] de Haan HG, Bezemer ID, Doggen CJM, Le Cessie S, Reitsma PH, Arellano AR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. *Blood*. 2012;120:656–63.

[24] Germain M, Chasman DI, de Haan H, Tang W, Lindström S, Weng LC, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *Am J Hum Genet*. 2015;96:532–42.

[25] Morange P-E, Suchon P, Trégouët D-A. Genetics of venous thrombosis: update in 2015. *Thromb Haemost*. 2015;114:910–9.

[26] Heit JA, Cunningham JM, Petterson TM, Armasu SM, Rider DN, De Andrade M. Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism. *J Thromb Haemost*. 2011;9:1133–42.

[27] Bruzelius M, Bottai M, Sabater-Lleal M, Strawbridge RJ, Bergendal A, Silveira A, et al. Predicting venous thrombosis in women using a combination of genetic markers and clinical risk factors. *J Thromb Haemost*. 2015;13:219–27.

[28] Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. *J Thromb Haemost*. 2014;12:1593–600.

[29] Smith NL, Rice KM, Bovill EG, Cushman M, Bis JC, McKnight B, et al. Genetic variation associated with plasma von Willebrand factor levels and the risk of incident venous thrombosis. *Blood*. 2011;117:6007–11.

[30] Weingarz L, Schwonberg J, Schindewolf M, Hecking C, Wolf Z, Erbe M, et al. Prevalence of thrombophilia according to age at the first manifestation of venous thromboembolism: results from the MAISTHRO registry. *Br J Haematol*. 2013;163:655–65.

[31] Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex difference in risk of second but not of first venous thrombosis: paradox explained. *Circulation*. 2014;129:51–6.

[32] Scheres LJJ, Van Hylckama Vlieg A, Cannegieter SC. Sex-specific aspects of venous thromboembolism: what is new and what is next? *Res Pract Thromb Haemost*. 2022;6:e12722. https://doi.org/10.1002/rth2.12722

[33] Norwegian Institute of Public Health. Medical Birth register - statistical bank; 2023. http://statistikkbank.fhi.no/mfr/index.jsp?headers=fodselstidspunkt_aar&headers=virtual&virtualsubset=afodsel_value+-+p_tmorsalder_kat_k8_null_value&v=2&stubs=mors_bosted_fylke&measure=common&fodselstidspunkt_aarsubset=2022&measuretype=4&study=http%3A%2F%2F10.0.3.47%3A80%2Fobj%2FfStudy%2Ff3a.mors.alder&cube=http%3A%2F%2F10.0.3.47%3A80%2Fobj%2FfCube%2Ff3a.mors.alder_C1&mors_bosted_fylkesubset=0000%2C01+-+14&mode=cube&top=yes. [accessed February 27, 2024].

[34] Eriksen EF, Moen MH, Iversen OE. Estrogens in menopause – time to change the guidelines?. Article in Norwegian. *Tidsskr Nor Laegeforen*. 2018;138. https://doi.org/10.4045/tidsskr.17.1059

[35] Braekkan SK, Borch KH, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: the Tromso Study. *Am J Epidemiol*. 2010;171:1109–15.

[36] Flinterman LE, Van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. *J Thromb Haemost*. 2015;13:548–54.

[37] Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. *Obesity (Silver Spring)*. 2011;19:402–8.

[38] Witte JS, Visscher PM, Wray NR. The contribution of genetic variants to disease depends on the ruler. *Nat Rev Genet*. 2014;15:765–76.

[39] Rockhill B, Weinberg CR, Newman B. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. *Am J Epidemiol*. 1998;147:826–33.

[40] Jiang T, Gill D, Butterworth AS, Burgess S. An empirical investigation into the impact of winner's curse on estimates from Mendelian randomization. *Int J Epidemiol*. 2023;52:1209–19.

Paper IV

Body height and risk of venous thromboembolism in men versus women

Carl Arne Løchen Arnesen[1,2] Kristian Hveem[3,4,5], Maiken E. Gabrielsen[3], John-Bjarne Hansen[1,2], Sigrid K. Brækkan[1,2]

[1]Thrombosis Research Center (TREC), Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway
[2]Thrombosis Research Group (TREC), Department of Clinical Medicine, UiT-The Arctic University of Norway, Tromsø, Norway
[3]HUNT Center for Molecular and Clinical Epidemiology, Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway
[4]HUNT Research Center, Department of Public Health and Nursing, Norwegian University of Science and Technology, Levanger, Norway
[5]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway.

Running title: Body height and risk of venous thromboembolism in men versus women

Keywords: Venous Thromboembolism, risk factors, sex differences, body height, epidemiology

Word count abstract: 249

Word count main text: 3257

Number of tables: 4

Number of figures: 2

Supplementary tables: 1

Supplementary appendix: 0

Number of references: 28

Correspondence to: Carl Arne Løchen Arnesen, Thrombosis Research Group (TREC), Department of Clinical Medicine, UiT – The Arctic University of Norway
Address: Department of Clinical Medicine, UiT – The Arctic University of Norway, N-9037 Tromsø, Norway
Email: carl.a.arnesen@uit.no, telephone +47 936 76 689

Abstract

Background: Body height is associated with venous thromboembolism (VTE) and may contribute to differences in VTE risk in men versus women.

Aims: To investigate the risk of VTE according to body height in men and women, and assess VTE risk in men versus women after adjustment for height in young, middle-aged, and elderly individuals.

Methods: Participants of the Tromsø Study (1994-2020) and the Nord-Trøndelag Health Study (1995-2019) formed the study cohort (n=114,567). Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) of VTE per 10 cm increase in body height in men and women. VTE risk in men versus women was estimated in the age groups 19-49, 50-74 and ≥75 years before and after adjustment for height.

Results: Taller stature was associated with increased VTE risk in both men (HR: 1.34, CI: 1.25-1.44) and women (HR: 1.23, CI: 1.13-1.33). In the middle-aged, the risk was higher in men than in women (HR: 1.45, CI: 1.32-1.60), but diminished after adjustment for height (HR 0.98, CI 0.85-1.13). In the young (HR: 0.87, CI 0.70-1.08) and elderly (HR: 1.08, CI: 0.97-1.20) there was no difference in VTE risk in men versus women before adjustment, while the risk was higher in women after height adjustment (HR: 0.60, CI: 0.44-0.83 and HR: 0.83, CI: 0.71-0.97, respectively).

Conclusions: Taller stature was a risk factor for VTE in men and women. The risk of VTE in men versus women was substantially affected by adjustment for body height in all age groups.

Introduction

Venous thromboembolism (VTE) is a severe, potentially life-threatening disease affecting 8-9% of all individuals during their lifetime (1, 2). Although the lifetime risk of VTE appears to be similar in men and women (1), the incidence rate across the sexes varies substantially with age, suggesting that the risk factor profiles vary in men and women. In the younger population (<50 years), women have a higher risk of VTE than men, which is largely attributed to reproductive risk factors like pregnancy and oral contraception (1, 3, 4). Among middle-aged individuals (50-75 years), men have a higher risk than women, but the reasons for the observed differences are not fully elucidated (1, 5-7).

Several studies have shown an association between body height and VTE risk in men, while the findings have been somewhat inconsistent in women (6, 8-11). The risk of VTE surges with increasing body height, and the more pronounced association observed in men is presumably explained by the fact that men generally achieve a taller stature than women (6, 8, 10). Based on this, it has been suggested that differences in VTE risk in men versus women could be attributed to differences in body height. To our knowledge, only one previous study has investigated the effect of body height on sex-specific VTE risk. In a Danish cohort of 56,014 middle-aged individuals (50-64 years), Severinsen et al. reported a higher crude incidence rate of VTE in men compared with women (incidence rate ratio [IRR]: 1.55), which was substantially reduced after adjustment for body height (IRR: 0.82) (6). This indicates that height may partially explain the difference in VTE risk between the sexes in this age group. To our knowledge, no study has explored the impact of body height on the risk of VTE in men versus women in the young and the elderly. This would be of particular interest, since the risk of VTE in men versus women is known to vary over the life span (1, 12, 13). In this study, we therefore aimed to investigate the risk of VTE according to body height in men and women in a large population-based cohort, and to investigate the risk of VTE in men versus women after adjustment for body height in young, middle-aged and elderly individuals.

Methods and results

Study population

The study population consisted of all participants from the fourth, fifth, sixth and seventh surveys of the Tromsø Study (1994-1995, 2001-02, 2007-08, 2015-16), and the second and third (1995-1997, 2006-08) surveys of the Trøndelag Health (HUNT) study. Both the Tromsø Study and HUNT are Norwegian population-based cohorts comprising inhabitants of Tromsø Municipality and the former Nord-Trøndelag county, respectively. In total, 36,626 unique individuals aged 25-97 years attended at least one of the Tromsø studies. In the HUNT2 and 3 surveys, 78,959 unique individuals aged 19-100 attended at least one survey. The two cohorts were merged into one large cohort (figure 1). Detailed methodology of both studies has been published in their cohort profile papers (14, 15).

Baseline measurements

Baseline information was obtained from physical examinations, blood samples and self-administered questionnaires in both cohorts. Measurement of body height and weight was conducted at the physical examination with participants wearing light clothes and no shoes. In Tromsø 4 and HUNT2, height was measured to nearest centimeter (cm) and weight was measured to the nearest half kilogram (kg), while Tromsø 5-7 and HUNT3 measured height to the nearest millimeter and weight to the nearest hectogram. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters (kg m^{-2}). Information on arterial cardiovascular disease (CVD; myocardial infarction, stroke, and angina) and smoking was collected via self-report questionnaires.

Follow-up and outcome assessment

Study participants were followed from the day of inclusion in their individual cohorts until the date of incident VTE, migration, death, or end of follow-up, whichever occurred first. In the Tromsø Study, VTE

events among the participants were identified by searching the hospital discharge diagnosis registry, the radiology procedure registry, and the autopsy registry at the University Hospital of North Norway (UNN). Trained health-care personnel reviewed the medical records, and the adjudication criteria were signs and symptoms of DVT or PE, combined with objective confirmation by a radiological procedure that resulted in treatment unless contraindications were present. In the HUNT Study, VTE events were identified by searching the discharge diagnosis registry and the radiology procedure registry at two local hospitals (Levanger and Namsos) and the discharge diagnosis registry at the tertiary-care center in the region, St. Olavs Hospital in Trondheim. The medical records were reviewed by health-care personnel, and the diagnosis criteria for VTE were symptomatic DVT or PE confirmed by a radiological procedure. Further description of the process of VTE identification in the cohorts can be found elsewhere (16, 17). The geographically well-defined areas of these cohorts, with only a few hospitals serving the entire regions, makes follow-up on disease development feasible, and enables a high degree of completeness on outcome data.

VTE events were classified as either isolated DVT or PE (±DVT), and as unprovoked or provoked depending on the presence of provoking factors at the time of diagnosis. In the Tromsø Study, provoking factors were: surgery or trauma (within the previous 8 weeks), acute medical conditions (ischemic stroke, acute myocardial infarction or major infectious disease), active cancer, marked immobilization (confined to wheelchair, bedrest ≥3 days or long-distance travel for ≥4 days within the previous 14 days), or another provoking factor described by a medical doctor in the medical record. In the HUNT3 study, the definition of provoking factors was the same as in the Tromsø study. In the HUNT2 study, the definition of provoking factors differed slightly and included: surgery or trauma, cancer (active at the time of event or within 6 month after the event), pregnancy or puerperium at the time of the event, or use of oral contraceptives at the time of the event or up to one month prior to the event, marked immobilization like paralysis, paresis, lengthy bedrest because of acute medical illness or >8 hour travel within the 3 months before the event.

Statistical analysis

Stata version 18.0 (Stata Corp, College Station, TX, USA) was used to perform the statistical analyses. Baseline characteristics were reported for men and women separately. Person-years of follow-up were accumulated from the date of enrolment until the date of incident VTE, migration, death or to the end of the study period (Tromsø Study: December 31, 2020; HUNT Study: December 31, 2019). Age served as time scale in the time-to-event analyses, with the age at enrolment defined as entry time. Cox-proportional hazards regression models were used to estimate sex-specific hazard ratios (HR) with 95% confidence intervals (CI) for VTE in men and women according to 5-cm body height categories before and after adjustment for BMI. The 166-170 cm category was used as reference group for both sexes to enable direct comparison between men and women as well as with an earlier study on body height and VTE risk (9). The lowest height category cut-off was ≤155 cm for both sexes, while the tallest height category cut-offs were ≥186 cm in women and ≥196 cm in men. In addition, we assessed the HR of VTE per 10 cm increase in body height in men and women. Lastly, we modeled height as a continuous variable, used 166 cm as reference value and constructed BMI-adjusted restricted cubic splines with four knots for both sexes to further gauge the potential of a non-linear association between VTE risk and body height.

Next, we divided the population into age categories (19-49 years, 50-74 years and ≥75 years, respectively). Sex-specific incidence rates (IRs) were calculated as the total number of events divided by the total person-time at risk in each age category and reported as the number of events per 1000 person-years (PYs). BMI-adjusted Cox regression models were used to assess the HR of VTE in men versus women before (model 1) and after adjustment of body height (model 2) in each age category. We also estimated the hazard ratios when taking the competing risk of death (CROD) into account (supplementary table 1). Lastly, we estimated the hazard ratios of unprovoked and provoked VTE for every age category and adjusted for body height.

Results

Among the 115,585 cohort participants, 52 were excluded due to emigration before the start of follow-up, 222 due to a previous VTE, and 744 due to missing values on body height and weight.

Baseline characteristics in women (n=60,438) and men (n=54,129) included in the study are displayed in table 1. Differences were observed in mean height (164.2 cm in women, 177.5 cm in men), weight (69.8 kg in women, 83.3 kg in men) and history of arterial cardiovascular diseases (5.1% in women, 8.6% in men). Median follow-up time was 22.7 years in women and 21.9 years in men, and 1,768 and 1,713 first-time VTE events were identified in women and men during follow-up, yielding an overall VTE incidence rate per 1,000 person-years of 1.64 (95% CI: 1.57-1.72) in women and 1.85 (95% CI: 1.76-1.94) in men. The proportion of DVTs (53.1% and 52.2%) and PEs (46.9% and 47.8%), as well as unprovoked (43.2% and 46.6%) and provoked (56.8% and 53.4%) VTEs, were similar in women and men (Table 1).

The risk of VTE increased with increasing body height in both women (Fig. 2A) and men (Fig. 2B). Similarly, the risk of VTE increased gradually per 5 cm category in both sexes compared to the reference category (166-170 cm) (Table 2). Women in the ≥186 cm body height category had a 4-fold higher risk (HR: 4.27, 95% CI:1.06-17.13) of VTE compared with the reference, and men in the ≥196 cm group had a 3.5-fold higher risk (HR 3.47, 95% CI:1.89-6.38) compared with the reference category. When body height was modeled as a continuous variable, the HR per 10 cm increase was 1.23 (95% CI: 1.13-1.33) in women and 1.34 men (95% CI: 1.25-1.44).

Table 3 presents the risk of VTE in men versus women in the young, middle-aged and elderly (age groups: 19-49 years, 50-74 years and ≥75 years). The IRs per 1000 PY increased by age groups in both men and women. In the group 19-49 years, the VTE risk was similar in men and women before adjustment for body height (HR for men vs. women: 0.87, 95% CI:0.70-1.08), while after adjustment, the risk was 1.5-fold higher in women than in men (HR for men vs. women: 0.60, 95% CI: 0.44-0.83). In the group 50-74 years, the risk was significantly higher in men before adjustment for body height (HR:

1.45, 95% CI: 1.32-1.60), but risk difference between sexes disappeared after adjustment for body height (HR: 0.98, 95% CI: 0.85-1.13). Among people aged 75 years and above, the risk was similar in men and women before adjustment for body height (HR:1.08, 95% CI: 0.97-1.20). After adjustment for body height, the risk was lower in men compared to women (HR: 0.83, 95% CI 0.71-0.97). The risk of VTE in men versus women before and after adjustment for body height showed similar patterns when taking the competing risk of death into account (supplementary table 1).

The association between unprovoked and provoked VTE in men versus women before and after adjustment for body height in young, middle-aged and elderly is shown in Table 4. These results showed similar patterns as the results for overall VTE. For unprovoked VTE, the risk in men versus women was highest in the middle-aged group before adjustment (HR: 1.72) and was substantially reduced after adjustment (HR:1.09). Similarly, for provoked VTE, the risk in men was highest among the middle aged before adjustment (HR:1.28) and was reduced after adjustment for body height (HR: 0.91).

Discussion

In this large population-based cohort, we confirmed that taller stature is associated with increased risk of VTE in both men and women. Among the middle-aged, the risk of VTE was higher in men compared with women, but the sex difference disappeared after adjustment for body height. In the younger and older age groups, the risk of VTE was similar in men and women before adjustment for body height, but a higher risk was found in women after adjustment. Our findings indicate that differences in body height impacts the VTE risk in men versus women in all age groups.

Although earlier studies have convincingly shown that increasing body height is a risk factor for VTE in men (7-10, 18), the results from studies in women have been less clear (8-10). In the MEGA case-control study, which included 4464 VTE cases and 5803 controls aged <70 years, a dose-response-relationship between increasing body height and VTE-risk was found in men, while the association was

weaker and not statistically significant in women (9). Similarly, in a previous report from the Tromsø cohort (n=26,727 with 462 VTEs), we showed a robust association between tall stature and VTE in men (HR per 10 cm increase in body height: 1.34, CI: 1.09-1.64), while the association was less pronounced in women (HR: 1.13, CI: 0.91-1.40). The observed weak association between body height and VTE in women in these studies could be explained by limited sample size, and thereby a limited number of women in the extremes of body height. In the Iowa Women's Health study (19), a cohort of 40,377 women aged 55-69 years, a 1.8-fold higher risk of VTE was observed in those ≥66 inches (167.6 cm) tall compared to those <62 inches (157.5 cm). Furthermore, longer leg-length was associated with VTE in both men and women aged ≥45 years in the Longitudinal Study of Thromboembolism Etiology (LITE) cohort (20). A Swedish registry-based study including 1.6 million men and 1 million women reported a clear association between body height and VTE in both sexes, where VTE risk in men ≥190 cm was 2.9-fold compared to men <160 cm, and VTE risk in women ≥185 cm was 3.2-fold compared to women <155 cm (18). Accordingly, we confirmed that increasing body height is a risk factor for first-time VTE in both men and women in a large cohort with a wide age span (19-98 years) and objectively assessed body height and VTE events.

It has been suggested that body height could contribute more to the VTE risk in men than in women because men achieve a taller stature. In the Danish Diet Cancer and Health (DCH) study, which consisted of 29,340 women and 26,674 men aged 50-64 years at inclusion, the crude IRR of VTE in men versus women was 1.55 but was attenuated to 0.82 after adjustment for difference in body height (6), suggesting that the higher risk of VTE in men in this age group was mainly explained by differences in body height. Since the risk of VTE in men versus women differs across age groups, and many of the studies reporting a higher risk of VTE in men have consisted of middle-aged participants at the time of inclusion (1, 5, 21, 22), we additionally set out to explore the impact of body height on the VTE risk in men versus women in the young and elderly population. In agreement with the DCH study, we found a higher VTE risk in men than in women among those aged 50-74 years, which diminished after adjustment for body height. In those 19-49 years, there was a slight inverse association (i.e., men had

a lower risk than women), which became substantially stronger after adjustment for body height, indicating that body height contributes to increase the VTE risk more in men than in women also in this age group. Similarly, among the elderly (≥75 years), we found no difference between the sexes before adjustment for body height, but the VTE risk was higher in women than in men after adjustment. These findings suggest that the risk of VTE is mediated through body height to a larger extent in men than in women in all age groups.

Mendelian randomization, using genetically predicted height as an instrumental variable, have supported that body height is a causal risk factor for VTE (23). Yet, the mechanisms by which body height increases the VTE risk are not fully established. Using a co-sibling design, Zoller et al. showed that the association between height and VTE was not confounded by familial genetic or environmental factors (18). Furthermore, Cushman and coworkers reported that markers of inflammation and hypercoagulability did not mediate the association between body height and VTE in the LITE cohort (24). Although height is associated with increased risk of cancer, the strong association between height and unprovoked VTE supports that the relationship is not explained by cancer-related VTE (8, 24). The association between height and VTE could be related to changes in blood flow. Reduced venous return, larger venous surface area, or longer distance between venous valves in taller people are features that may render blood more prone to stasis (20). Further, the number of venous valves is known to vary among individuals (25), and it has been hypothesized that taller people might have more valves than individuals of shorter stature (18, 20), thus being more susceptible to thrombus formation.

The main strengths of the present study are its prospective design, the high attendance rates and recruitment from the general population in both cohorts, which made it possible to contrast many categories of body height, as well as the long-term follow-up and thoroughly validated VTE events from the regional hospitals covering the catchment areas of the cohorts. All hospitals used radiological imaging to confirm the VTE diagnosis and are the sole treatment centres for VTE in their region (both inpatient and outpatient care), which increases the likelihood of a complete VTE registration.

Furthermore, the high age diversity, ranging from 19-98 years at baseline makes the results more applicable to the general population. Additionally, height was measured by health care professionals and since adult height is a non-modifiable risk factor there is little risk of misclassification and regression dilution bias. Our study population is mainly of Caucasian descent, which lowers the risk of population stratification, but limits the generalizability to other ethnicities. Our study was limited by few subjects that were either very tall or very short, which affected the statistical power in these groups. We did not have complete baseline information on previous VTE among the study participants. Therefore, some of the subjects who were included as healthy participants could have had a previous VTE and should preferably have been excluded at baseline. However, since this proportion would be relatively small, it is not expected to affect our results. Unfortunately, we did not have information on leg length which has been proposed as a more accurate measure of VTE risk than body height (9, 20). There is also potential for birth cohort effects due to a general increase in median height over time in our study population (26). Further, we do not have genetic information on all participants, and chromosomal anomalies, such as XYY and XXY is associated with both increased VTE risk and taller stature (27, 28). However, considering the rarity of these syndromes and the linear increase of VTE risk by increasing stature, it is unlikely that such anomalies have affected the estimates in any considerable way.

In conclusion, taller stature was a risk factor for VTE in men and in women. The risk of VTE in men versus women varied across age groups, but was substantially affected by adjustment for body height in all age groups. Our findings indicate that the risk of VTE is mediated through body height to a larger extent in men than in women in all age groups.

Author contributions: conception and design: JBH and SKB; Data collection: JBH, KH; Statistical analyses: CALA, SKB; Interpretation of results: CALA, JBH, KH, MEG, SKB; Draft of Manuscript: CALA; Critical revision of manuscript: JBH, SKB, KH, MEG.

Conflicts of Interest: There are no conflicts of interest by any of the authors.

Acknowledgements

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. We want to thank clinicians and other employees at Nord-Trøndelag Hospital Trust for their support and for contributing to data collection in this research project.

References

1. Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. Eur J Epidemiol. 2022;37(2):195-203.
2. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, et al. Lifetime Risk of Venous Thromboembolism in Two Cohort Studies. The American Journal of Medicine. 2016;129(3):339.e19-.e26.
3. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Bmj. 2009;339:b2890.
4. Virkus RA, Løkkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard Ø. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb Haemost. 2011;106(2):304-9.
5. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. The American Journal of Medicine. 2004;117(1):19-25.
6. Severinsen MT, Johnsen SP, Tjønneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: A Danish follow-up study. European Journal of Internal Medicine. 2010;21(4):268-72.
7. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the Incidence of Deep Vein Thrombosis and Pulmonary Embolism. Archives of Internal Medicine. 1998;158(6):585.
8. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body Height and Risk of Venous Thromboembolism: The Tromso Study. American Journal of Epidemiology. 2010;171(10):1109-15.
9. Flinterman LE, Van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. Journal of Thrombosis and Haemostasis. 2015;13(4):548-54.
10. Pomp ER, Le Cessie S, Rosendaal FR, Doggen CJM. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. British Journal of Haematology. 2007;139(2):289-96.
11. Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. Journal of Thrombosis and Haemostasis. 2014;12(10):1593-600.
12. Arshad N, Isaksen T, Hansen J-B, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. European Journal of Epidemiology. 2017;32(4):299-305.
13. Cushman M. Epidemiology and Risk Factors for Venous Thrombosis. Seminars in Hematology. 2007;44(2):62-9.
14. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø Study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scandinavian Journal of Public Health. 2022;50(7):919-29.
15. Åsvold BO, Langhammer A, Rehn TA, Kjelvik G, Grøntvedt TV, Sørgjerd EP, et al. Cohort Profile Update: The HUNT Study, Norway. Int J Epidemiol. 2023;52(1):e80-e91.

16. Borch KH, Nyegaard C, Hansen J-B, Mathiesen EB, Njølstad I, Wilsgaard T, et al. Joint Effects of Obesity and Body Height on the Risk of Venous Thromboembolism. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011;31(6):1439-44.
17. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. Journal of Thrombosis and Haemostasis. 2007;5(4):692-9.
18. Zöller B, Ji J, Sundquist J, Sundquist K. Body Height and Incident Risk of Venous Thromboembolism. Circulation: Cardiovascular Genetics. 2017;10(5).
19. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR, et al. Correlates and Consequences of Venous Thromboembolism: The Iowa Women's Health Study. American Journal of Public Health. 2010;100(8):1506-13.
20. Lutsey PLC, Mary, Heckbert SR, Tang W, Folsom AR. Longer legs are associated with greater risk of incident venous thromboembolism independent of total body height. Thrombosis and Haemostasis. 2011;106(07):113-20.
21. Scheres LJJ, Van Hylckama Vlieg A, Cannegieter SC. Sex-specific aspects of venous thromboembolism: What is new and what is next? Research and Practice in Thrombosis and Haemostasis. 2022;6(4):e12722.
22. Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex Difference in Risk of Second but Not of First Venous Thrombosis. Circulation. 2014;129(1):51-6.
23. Roetker NS, Armasu SM, Pankow JS, Lutsey PL, Tang W, Rosenberg MA, et al. Taller height as a risk factor for venous thromboembolism: a Mendelian randomization meta-analysis. Journal of Thrombosis and Haemostasis. 2017;15(7):1334-43.
24. Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology. Thrombosis Research. 2016;144:127-32.
25. Moore HM, Gohel M, Davies AH. Number and location of venous valves within the popliteal and femoral veins – a review of the literature. Journal of Anatomy. 2011;219(4):439-43.
26. Arntsen SH, Borch KB, Wilsgaard T, Njølstad I, Hansen AH. Time trends in body height according to educational level. A descriptive study from the Tromsø Study 1979–2016. PLOS ONE. 2023;18(1):e0279965.
27. Berry ASF, Finucane BM, Myers SM, Abril A, Kirchner HL, Ledbetter DH, et al. Association of Supernumerary Sex Chromosome Aneuploidies With Venous Thromboembolism. JAMA. 2023;329(3):235.
28. Zöller B, Ji J, Sundquist J, Sundquist K. High Risk of Venous Thromboembolism in Klinefelter Syndrome. Journal of the American Heart Association. 2016;5(5):e003567.

Table 1: Baseline characteristics and characteristics at the time of the venous thromboembolism event in men and women

	Women	Men
Baseline characteristics	**n=60,438**	**n=54,129**
Age (years), Mean ± SD	48 ± 17	48 ± 16
Height (cm), Mean ± SD	164.2 ± 6.5	177.5 ± 6.9
Weight (kg), mean ± SD	69.8 ± 12.9	83.3 ± 12.9
BMI, Mean ± SD	25.9 ± 4.6	26.4 ± 3.6
Cardiovascular disease*, %	5.3	8.8
VTE characteristics	**n=1,768**	**n=1,713**
Age at VTE (years), Mean ± SD	74.6	70.2
Pulmonary embolism, %	46.9	47.8
Deep vein thrombosis, %	53.1	52.2
Unprovoked, %	43.2	46.6
Provoked, %	56.8	53.4

*Myocardial infarction, stroke, angina

Table 2: Hazard ratios (HR) for total venous thromboembolism according to categories of body height in men and women.

Women				
Height (cm)	**Person-years**	**Events**	**HR (95% CI)***	**HR (95% CI)****
0-155	83,817	234	0.87 (0.73-1.03)	0.81 (0.68-0.96)
156-160	201,143	396	0.85 (0.73-0.98)	0.82 (0.71-0.94)
161-165	330,784	558	0.99 (0.86-1.12)	0.97 (0.85-1.10)
166-170	285,716	373	ref.	ref.
171-175	134,648	160	1.13 (0.94-1.36)	1.16 (0.97-1.40)
176-180	34,829	38	1.27 (0.91-1.78)	1.32 (0.95-1.85)
181-185	4,190	7	2.28 (1.08-4.83)	2.41 (1.14-5.10)
≥186	475	2	3.68 (0.92-14.79)	4.27 (1.06-17.13)
Height per 10 cm	1,075,903	1,768	1.17 (1.08-1.27)	1.23 (1.13-1.33)
Men				
Height (cm)	**Person-years**	**Events**	**HR (95% CI)***	**HR (95% CI)****
0-155	1,027	4	1.83 (0.68-4.91)	1.80 (0.67-4.85)
156-160	4,303	9	0.78 (0.40-1.52)	0.78 (0.40-1.52)
161-165	25,999	61	0.94 (0.70-1.24)	0.93 (0.70-1.24)
166-170	97,275	209	ref.	ref.
171-175	212,022	381	1.00 (0.84-1.18)	1.00 (0.85-1.19)
176-180	272,312	504	1.26 (1.07-1.48)	1.27 (1.08-1.49)
181-185	199,326	349	1.43 (1.20-1.70)	1.44 (1.21-1.72)
186-190	88,808	147	1.61 (1.30-1.99)	1.63 (1.31-2.02)
191-195	21,479	38	2.11 (1.49-2.99)	2.16 (1.52-3.06)
≥196	4,440	11	3.37 (1.83-6.19)	3.47 (1.89-6.39)
Height per 10 cm	926,991	1,713	1.33 (1.23-1.43)	1.34 (1.25-1.44)

*Adjusted for age (as time scale)

**Adjusted for age (as time scale) and body mass index

Table 3: Risk of venous thromboembolism in men versus women**.** Incidence rate (IR) with 95% Confidence Intervals (CI) per 1000 person-years (PY) and hazard ratio (HR) with 95% CI.

Age Range	PY	Events	IR (95% CI)	Model 1 HR (95% CI)*	Model 2 HR (95% CI)**
Ages 19-49					
Women	398,429	183	0.46 (0.40-0.53)	Ref.	Ref.
Men	339,657	145	0.43 (0.36-0.50)	0.87 (0.70-1.08)	0.60 (0.44-0.83)
Ages 50-74					
Women	515,604	719	1.39 (1.30-1.50)	Ref.	Ref.
Men	475,914	967	2.03 (1.91-2.16)	1.45 (1.32-1.60)	0.98 (0.85 -1.13)
Ages ≥75					
Women	161,870	866	5.35 (5.01-5.72)	Ref.	Ref.
Men	111,421	601	5.39 (4.98-5.84)	1.08 (0.97-1.20)	0.83 (0.71-0.97)

*Adjusted for age (as time scale) and body mass index (BMI)

**Adjusted for age (as time scale), BMI and body height per 1 cm

Table 4: Risk of unprovoked and provoked venous thromboembolism in men versus women**.** Incidence rates (IR) and hazard ratios (HR) with 95% Confidence Intervals (CI).

Age Range	Person-years	Events	IR (95% CI)	Model 1 HR (95% CI)*	Model 2 HR (95% CI)**
VTE Unprovoked					
19-49 years					
Women	398,429	86	0.22 (0.17-0.27)	Ref.	Ref.
Men	339,657	72	0.22 (0.17-0.27)	0.93 (0.68-1.27)	0.62 (0.39-0.99)
50-74 years					
Women	515,604	289	0.56 (0.50-0.63)	Ref.	Ref.
Men	475,914	459	0.96 (0.88-1.06)	1.72 (1.48-1.99)	1.09 (0.88-1.35)
≥75 years					
Women	161,870	389	2.40 (2.18-2.65)	Ref.	Ref.
Men	111,421	267	2.40 (2.12-2.70)	1.08 (0.93-1.21)	0.90 (0.71-1.14)
VTE Provoked					
19-49 years					
Women	398,429	97	0.24 (0.20-0.30)	Ref.	Ref.
Men	339,657	73	0.21 (0.17-0.27)	0.82 (0.61-1.11)	0.58 (0.37-0.91)
50-74 years					
Women	515,604	430	0.83 (0.76-0.92)	Ref.	Ref.
Men	475,914	508	1.07 (0.98-1.16)	1.28 (1.12-1.45)	0.91 (0.75 -1.09)
≥75 years					
Women	161,870	477	2.95 (2.69-3.22)	Ref.	Ref.
Men	111,421	334	3.00 (2.69-3.34)	1.06 (0.92-1.23)	0.77 (0.62-0.95)

*Adjusted for age (as time scale) and body mass index (BMI)

**Adjusted for age (as time scale), BMI and body height per 1 cm

Figure 1. Composition of study population

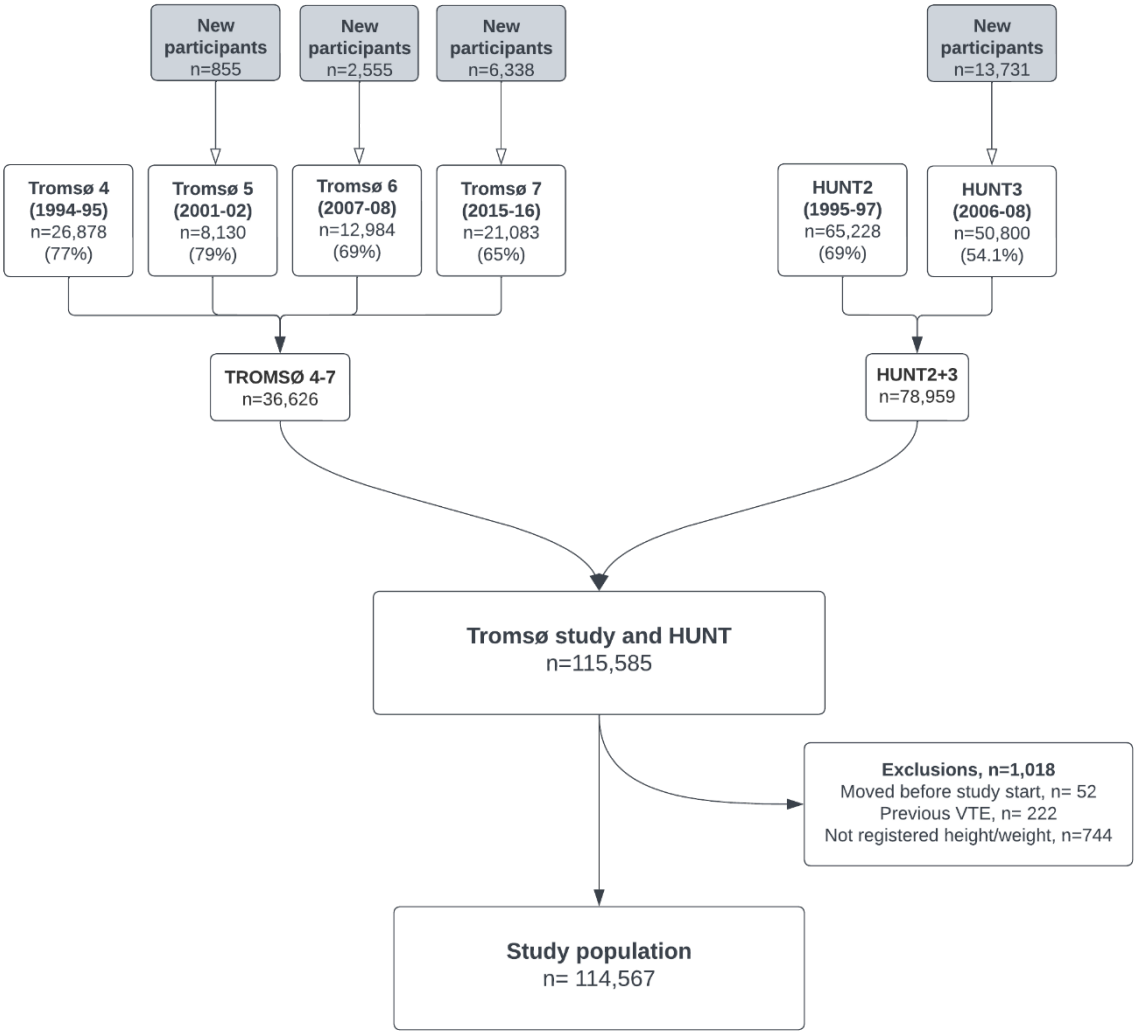
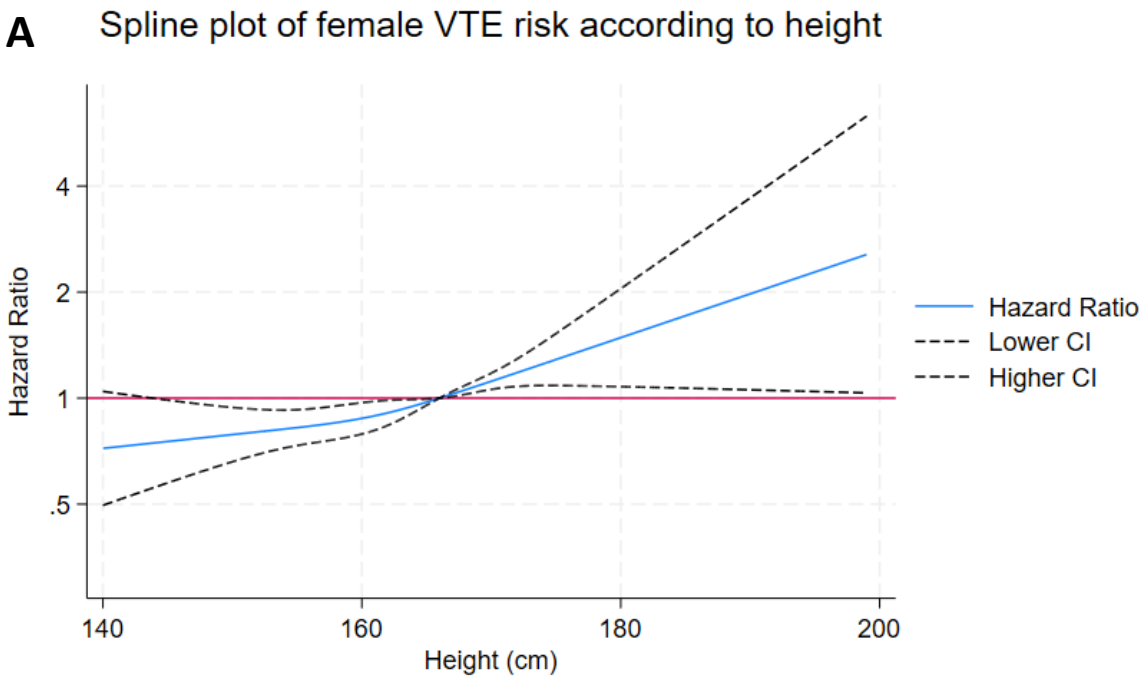
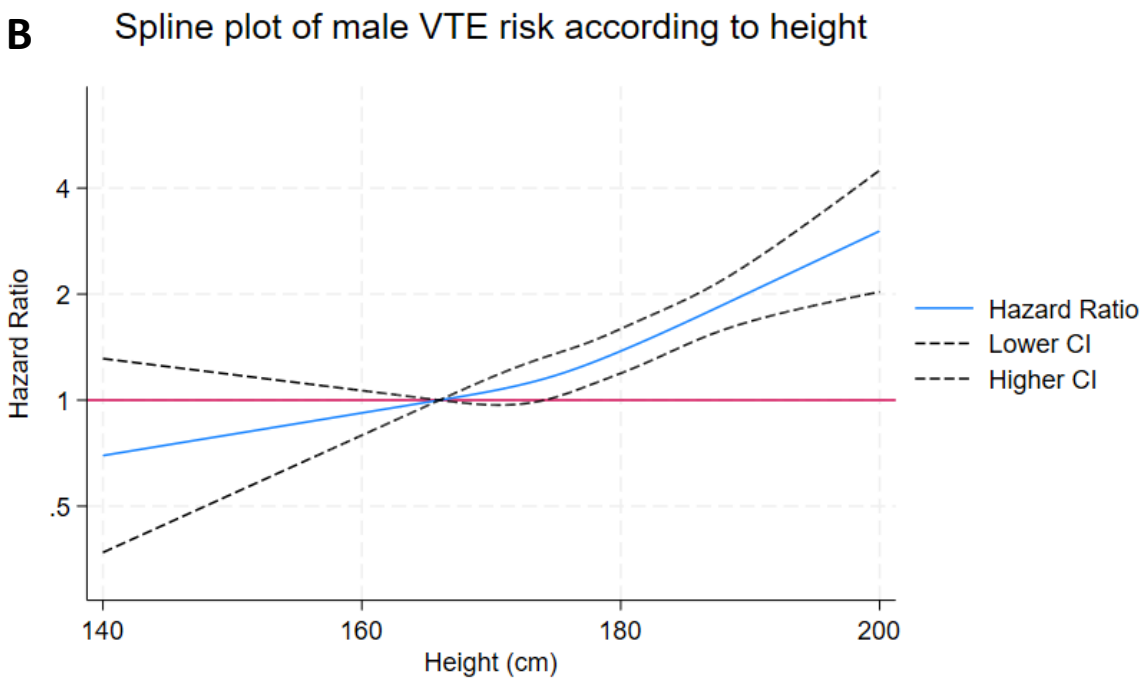


Figure 2. Spline plot of VTE risk according to body height (cm) in (A) women and (B) men. Hazard ratios with 95% Confidence Intervals (CI). 166 cm served as reference value for both sexes. The spline plots were adjusted for age (as time scale) and BMI.





Supplementary table 1: Risk of venous thromboembolism in men versus women including death as a competing event**.** Hazard ratio (HR) with 95% Confidence Intervals (CI).

Age Group	Model 1 HR (95% CI)*	Model 2 HR (95% CI)**
Ages 19-49		
Women	Ref.	Ref.
Men	0.87 (0.70-1.08)	0.60 (0.44-0.83)
Ages 50-74		
Women	Ref.	Ref.
Men	1.41 (1.28-1.55)	0,96 (0.83 -1.10)
Ages 75-->		
Women	Ref.	Ref.
Men	0.89 (0.80-0.98)	0.73 (0.62-0.85)

*Adjusted for age (as time scale), body mass index (BMI) and competing risk of death

**Adjusted for age (as time scale), BMI, competing risk of death and body height per 1 cm