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Obesity, body height and risk of venous thromboembolism

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CONTENTS

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SUMMARY

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the third most common cardiovascular disease after myocardial infarction (MI) and stroke, with an incidence that is stable or even slightly increasing. To be able to tailor targeted treatment and prevention in the future, further insight into risk factors and the pathophysiology of VTE is needed. Obesity, as well as a tall stature, are well-known and substantial risk factors for VTE, but the underlying mechanisms behind these associations are not fully understood. The aims of this thesis were to investigate how different patterns of body fat distribution, levels of obesity-related cardiovascular risk factors and chronic, low-grade inflammation influenced the risk of venous and arterial thrombosis. Further, we wanted to investigate whether changes in body weight over time was associated with VTE risk. Finally, we sought to explore if the combined presence of a tall stature and genetic pro-thrombotic risk factors yielded synergistic effects on the risk of VTE.

The study populations in this thesis were recruited from the third (1986-87) through the sixth (2007-2008) surveys of the Tromsø study, a large population-based cohort. Exposure information was obtained through self-administered questionnaires, blood samples and physical examination. Incident VTE events during follow-up were registered and thoroughly validated.

In the first paper, we found that body fat distribution had a differential impact on venous and arterial thrombosis, where subjects with wide hips were at elevated risk of VTE but not MI. Further, cardiometabolic abnormalities such as insulin resistance, hypertension and dyslipidemia did not seem to mediate the increased risk of VTE in obesity as it does for MI. In the second paper, chronic low-grade inflammation assessed by C-reactive protein (CRP) appeared to be a shared pathway for the association between obesity and arterial and venous thrombosis, at least in women. However, the strengths of association were much weaker for VTE than for MI.

In the third paper, we showed that changes in body weight are associated with VTE risk independent of baseline body mass index (BMI). Subjects who gained more than 7.5 kgs between two surveys of the Tromsø study were at a 1.6-fold increased risk of VTE in the

years that followed compared to those who maintained a stable weight. Among subjects with a BMI ≥30 kg/m^2, those who gained most weight were at almost a four-fold increased risk.

Finally, in the fourth paper, we confirmed previous findings of an increased risk of VTE among subjects with a tall stature, where subjects above >80th percentile in body height were at a 2-fold increased risk of VTE. Likewise, the presence of prothrombotic genotypes was associated with VTE risk. However, in contrast to obesity, the combination of a tall stature and prothrombotic genotypes did not yield excess risk of VTE.

SAMMENDRAG

Venøs tromboembolisme (VTE) er en fellesbetegnelse for dyp venetrombose og lungeemboli. VTE er den tredje vanligste kardiovaskulære sykdommen etter hjerteinfarkt og hjerneslag, med en forekomst som er stabil eller til og med lett økende. For å kunne skreddersy målrettet behandling og forebygging i fremtiden er det essensielt å få ytterligere innsikt i risikofaktorer og årsaksmekanismer for sykdommen. Fedme, så vel som stor kroppshøyde, er kjente og betydelige risikofaktorer for VTE, men mekanismene som ligger bak er ikke fullstendig kartlagt. Formålet med denne avhandlingen var å undersøke hvordan ulike fedmemål, nivå av fedmerelaterte kardiovaskulære riskofaktorer og kronisk betennelse påvirket risiko for venøs og arteriell trombose. Videre ville vi undersøke om endringer i kroppsvekt over tid var forbundet med risiko for VTE. Til sist studerte vi hvorvidt stor kroppshøyde i kombinasjon med arvelige risikofaktorer for VTE førte til synergieffekter i risiko.

Studiepopulasjonene i denne avhandlingen ble rekruttert fra den tredje (1986-87) til den sjette (2007-08) Tromsøundersøkelsen. Informasjon om deltakerne ble innhentet gjennom spørreskjema, blodprøver og klinisk undersøkelse. Alle VTE-hendelser i oppfølgingstiden ble registrert og grundig validert.

I den første artikkelen så vi at ulike fedmemål hadde forskjellig innvirkning på risiko for VTE, hvor de med brede hofter hadde forhøyet risiko for VTE men ikke for hjerteinfarkt. Videre så vi at insulinresistens, høyt blodtrykk og andre metabolske forstyrrelser assosiert med fedme ikke påvirket risikoen for VTE på samme måte som for hjerteinfarkt. I den andre artikkelen så vi at kronisk betennelse, målt ved CRP, kan være en felles mekanisme for sammenhengen mellom fedme og arteriell og venøs trombose, i alle fall hos kvinner. Dog var sammenhengen betydelig svakere for VTE enn for hjerteinfarkt.

I den tredje artikkelen viste vi at endringer i kroppsvekt over tid var forbundet med økt risiko for VTE uavhengig av kroppsmasseindeks (BMI). Deltakere som gikk opp mer enn 7.5 kg i vekt mellom to undersøkelser hadde 1.6 gang så høy risiko for VTE sammenlignet med de som holdt vekta stabil. Blant deltakere som hadde BMI over 30 kg/m^2 i utgangspunktet, var en videre økning i vekt på mer enn 7.5 kg forbundet med fire ganger økt risiko for VTE.

Til sist bekreftet vi tidligere funn om at høye personer har økt risiko for VTE, hvor deltakere over 80-persentilen i høyde hadde doblet VTE-risiko. Også tilstedeværelse av kjente genetiske risikofaktorer var forbundet med økt risiko. Til forskjell fra hva som tidligere er beskrevet for fedme, fant vi ingen synergieffekt for kombinasjonen av stor kroppshøyde og genetiske risikofaktorer for VTE risiko.

LIST OF PAPERS

The thesis is based on the following papers:

I. Obesity measures and risk of myocardial infarction and venous thromboembolism.
Horvei LD, Brækkan SK, Mathiesen EB, Njølstad I, Wilgaard T, Hansen JB
Eur J Epidemiol. 2014 Nov; 29(11): 821-30

II. C-reactive protein, obesity and the risk of arterial and venous thrombosis.
Horvei LD, Grimnes G, Hindberg K, Mathiesen EB, Njølstad I, Wilsgaard T, Brox J, Brækkan SK, Hansen JB
J Thromb Haemost 2016 Aug; 14(8): 1561-71

III. Weight change and risk of venous thromboembolism: The Tromsø Study.
Horvei LD, Brækkan SK, Hansen JB
Plos One 2016 Dec 20; 11 (12)

IV. Joint effects of prothrombotic genotypes and body height on the risk of venous thromboembolism: The Tromsø Study.
Horvei LD, Brækkan SK, Smith EN, Solomon T, Hindberg K, Frazer KA, Rosendaal FR, Hansen JB
Manuscript

ABBREVIATIONS

VTE – Venous thromboembolism

DVT – Deep vein thrombosis

PE – pulmonary embolism

MI – Myocardial infarction

CRP – C-reactive protein

BMI – Body mass index

CVD – Cardiovascular disease

TF – Tissue factor

PAI-1 Plasminogen activator inhibitor-1

FVL – Factor V Leiden

SNP – Single nucleotide polymorphism

MEGA - the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study

HDL – High density lipoprotein

UNN – University Hospital of North Norway

WC – Waist circumference

HC – hip circumference

WHR – waist-hip ratio

WHtR – waist-height ratio

HR – Hazard ratio

RCT – randomized controlled trial

HUNT - Nord-Trøndelag Health Study

OR – Odds ratio

INTRODUCTION

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). A deep vein thrombosis is the formation of a blood clot most commonly occurring in the deep veins of the lower extremities, but other sites such as the veins of the upper extremities or intraabdominal veins may also be affected (1). Obstruction of venous return leads to pain, swelling and redness of the affected extremity, although some cases may present with few or no symptoms.

A pulmonary embolism is traditionally seen as a complication of a DVT, which occurs when parts of a clot, an embolus, breaks free and travels with the bloodstream to the lungs. However, during the recent years it has been suggested that blood clots may occur *de novo* in the arterial circulation of the lungs (2), or embolize from the right atrium in atrial fibrillation (3, 4). In fact, only about 40% of patients with PE present with a concurrent clinically detectable DVT (5, 6). Symptoms of a PE may range from mild pleuritic chest pain to grave dyspnea caused by cardiac decompensation or even cardiac arrest (7).

Anticoagulation therapy is the mainstay of VTE treatment while fibrinolytic agents are reserved for PEs with cardiac decompensation (8). Catheter-directed thrombolysis for extensive proximal DVTs probably reduces the risk of post-thrombotic syndrome, but it is associated with a risk of procedure-related complications and does not improve quality of life (9). Despite advances in treatment options, with the emergence of new anticoagulant drugs in the recent years, VTE remains a major contributor to global disease burden (10).

VTE is recognized as a complex, multifactor disease involving both environmental exposures as well as genetic and environmental interactions (11). Obesity is a well-established risk factor for VTE, as several studies have pointed to a 2-3 fold increased risk in obese subjects (12-16). The combination of obesity and other risk factors such as prothrombotic genetic factors or use of oral contraceptives result in dramatic synergies, with a 10- to 20-fold risk increase (14, 17). The prevalence of obesity is increasing throughout the world, described by the WHO as a “global epidemic” which causes an array of serious health disorders. Even though its association with VTE is well-known, the mechanisms by which obesity causes thrombosis remain unclear.

A tall stature has also been recognized as a risk factor for VTE, with similar strengths of associations than for obesity (18-21). Although it has been shown that venous hemodynamics are altered with increasing body height (22, 23), the underlying mechanisms between this association are not fully understood.

In order to prevent the wave of thrombotic events that accompanies the ongoing obesity epidemic, further insight into pathophysiological mechanisms and risk prediction is warranted.

Epidemiology of venous thromboembolism

VTE is the third most common life-threatening cardiovascular disease after myocardial infarction and ischemic stroke, with an annual incidence of 1-2 per 1000 person-years. The incidence increases steeply with advancing age (24). While the incidence rates for myocardial infarction (25, 26) and ischemic stroke (27) are decreasing, VTE incidence is stable or even slightly increasing (28, 29). One-month mortality rates range from 5-10 % after a first-time DVT and 8-16 after a first PE event (30-32). Pulmonary embolism is a leading preventable cause of death in hospitalized patients (33), and as much as 25 % of cases may present as sudden death (34). Removal of reversible provoking factors such as estrogen use in women reduces the risk of recurrence. Still, 10-30 % of patients with an unprovoked VTE experience a recurring event within 10 years after the first VTE diagnosis (35-37). Recurrences tend to occur at the same site as the index event (37-39), implicating that PE patients are at higher risk of a fatal recurrent event than DVT patients. Considerable morbidity is caused by the post-thrombotic syndrome, a condition characterized by chronic pain and swelling, which develops in 15-50 % of patients after a DVT (40-42). Furthermore, the risk of permanent work-related disability is increased by more than 50 % after a first unprovoked VTE, which probably largely can be attributed to the post-thrombotic syndrome (43). A dreaded long-term complication of PE, occurring in 2-5 % of the PE patients, is chronic thromboembolic pulmonary hypertension, a condition characterized by thrombus organization and fibrous stenosis in the pulmonary circulation. It is a disabling condition where symptoms include dyspnea, hypoxemia and right-sided heart failure (34, 44-46).

Obesity – an ongoing global epidemic

Obesity is generally defined as excessive fat accumulation in adipose tissue, to the extent that health may be impaired (47). There is no clear division between a normal and abnormal accumulation of body fat. According to the World Health Organization, a body mass index (BMI) of 25-29.9 kg/m^2 is indicative of overweight, and a BMI ≥ 30 kg/m^2 indicates obesity (47). However, BMI has some major flaws as a measure of body fat, as it does not take age, sex, bone structure, fat distribution or muscle mass into consideration. Furthermore, self-reported BMIs are notoriously inaccurate (48, 49). Other anthropometric measures (or ratios between these) do better predict cardiovascular disease (50-52) and are more highly correlated with an unfavorable metabolic profile (53). Still, BMI remains in use because of its simplicity and tradition.

The prevalence of obesity is increasing at an alarming rate worldwide in both developed and undeveloped countries, in children, adolescents and adults alike (47). The majority (53 %) of the adult population in the European Union are now overweight or obese, and the rate of obesity is exceeding 25 % in some EU countries (54) and 35 % in the United States (55).

A diversity of co-morbidities are related to obesity, but the relationship to type 2 diabetes is perhaps the strongest. The risk of type 2 diabetes increases with increasing BMI even within the normal BMI range, but the risk escalates with a BMI >30 kg/m^2 (56). Increased fat mass is a key feature in the metabolic syndrome, which is a set of risk factors including central obesity, insulin resistance, hypertension and dyslipidemia (57). When three of these criteria are met, the risk of cardiovascular disease is increased two-fold (57). Other obesity-related diseases include nonalcoholic fatty liver disease (58), gall bladder disease (59), sleep apnea (60) and osteoarthritis (61). Further, several cancer types such as colon, breast and gastric cancer are associated with obesity, even though the biological mechanisms underlying these associations are not well understood (62).

Interrelations between arterial and venous thrombosis

Arterial and venous thrombosis have traditionally been seen as two separate disease entities, with different pathophysiology and treatment. Atherosclerosis can be described as a chronic inflammatory disease (63). Arterial clots appear under high shear stress, as the disruption of an atherosclerotic plaque leads to the formation of a platelet-rich "white thrombus" (64) which is treated with anti-platelet drugs. Conversely, a venous thrombus is not preceded by a chronic phase. The venous "red thrombi", rich in fibrin and red blood cells most often are initiated in the hypoxic and static milieu of the venous valve pockets (65). Venous thrombi are typically treated with anticoagulant drugs (66).

However, after Prandoni and co-workers first published a case-control study where VTE cases had an odds ratio of 1.8 for the presence of carotid plaques compared to controls (67), a large body of evidence has established a clear link between arterial and venous thrombosis. In a large-scale Swedish autopsy study, there was a positive association between atherothrombosis and VTE (68). Later, Sørensen et al reported findings from a large-scale registry based study, where VTE patients were at increased risk for a subsequent cardiovascular event (69), and that patients with cardiovascular events were at (short-term) increased risk of VTE (70). Several other studies have shown similar increased risks of cardiovascular disease after a VTE event (71-74), and a meta-analysis published in 2010 concluded that the risk of an arterial thrombotic event (e.g. myocardial infarction (MI) or ischemic stroke) was 1.9-fold increased after a VTE (75). Results from registry-based linkage studies should however be interpreted with caution, as they often lack information about confounders and have limited validation of exposure and outcomes. A recent paper from the Tromsø study with detailed confounder information and validated outcomes confirmed that subjects with incident MI were at a transient increased risk of VTE, the risk being 4.8-fold elevated during the first 6 months after the MI event (76). Likewise, combined data from the prospective Diet, Cancer and Health study in Denmark and the Tromsø study revealed that women and young men with VTE had a higher risk of arterial thrombotic disease than those without VTE, with the risk being highest within the first year after the VTE event (77).

The observed association between cardiovascular disease (CVD) and VTE could be explained by a "cause and effect" relationship, where the occurrence of one disease entity directly

influences the risk of the other. Alternatively, a set of shared risk factors might increase the risk of both disease entities, independently from the occurrence of the events in themselves. The impact of traditional atherosclerotic risk factors on VTE risks have been studied, with somewhat conflicting results. However, in addition to advancing age, obesity and family history of myocardial infarction are the only risk factor that has consistently been associated with both disease entities (78, 79). Most prospective cohorts found no association between serum lipids, hypertension or diabetes (12, 13, 79, 80). Smoking was associated with VTE in some prospective studies (13, 17, 81), but not in others (12, 79, 80). Further, if shared risk factors could explain the observed associations, one would expect a permanent and not a transient increased risk of VTE after an MI and vice versa. It has been suggested that indirect causal factors, such as hospitalization, endovascular procedures and surgery following an MI may contribute to VTE risk (76, 82), and also disturbances in the cardiopulmonary circulation after MI might predispose to thrombus formation (83). Likewise, the fact that PE is a stronger predictor of MI than VTE might also be due to local disturbances in the cardiopulmonary circulation (77).

Pathophysiology of obesity-related thrombosis

General pathophysiology of VTE

In the 19th century, the legendary German physician Rudolph Virchow elucidated the etiology of pulmonary embolism, describing three broad categories of prothrombotic factors later known as "Virchow's triad" (figure 1) (84). The triad consists of (i) stasis or turbulence of blood flow, (ii) hypercoagulability and (iii) endothelial injury. Even though our understanding of thrombus formation has evolved since the days of Virchow, these principles still apply. Thrombi that form in veins are referred to as "red clots", meaning that they primarily consist of a fibrin network and trapped red blood cells, in contrast to the platelet-rich "white clots" seen in arterial thrombosis (66).

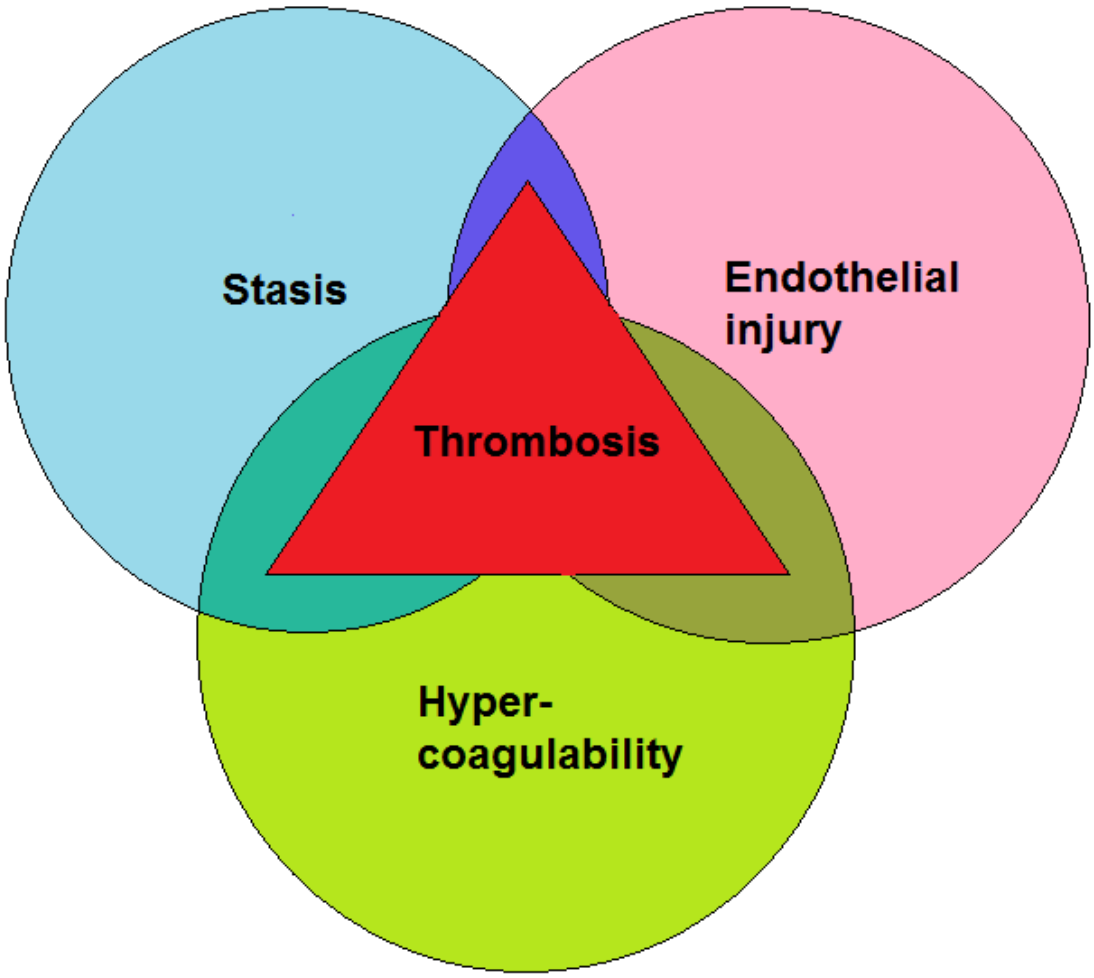

Figure 1. Virchow`s triad

The valve pockets of large veins are common sites for the initiation of venous thrombus formation, as blood is prone to irregular, vortical blood flow, stasis and intermittent hypoxia at these sites (figure 2) (85). When blood flow ceases, hypoxic blood trapped in the vortex leads to stimulation of the endothelium, resulting in accumulation of leukocytes, platelets and prothrombotic substances and procoagulant responses in the endothelium (65, 85-88). In fact, a study by Liu et al reported an association between VTE risk and the number of venous valves between the popliteal fossa and the ischial spine (89). The importance of stasis is further illustrated by the fact that immobilization, long-haul air travel and plaster cast treatment increase the risk of VTE (90).

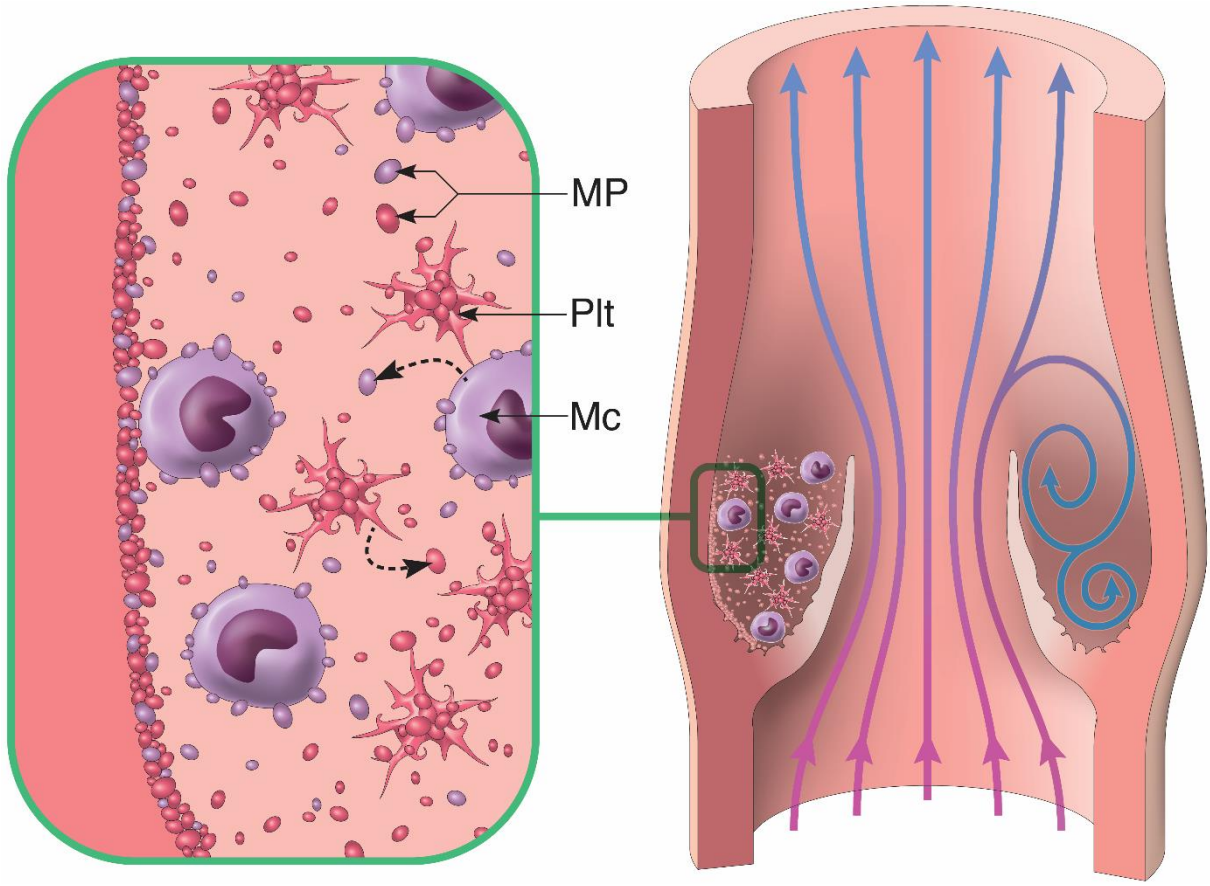

Figure 2. The valve pocket is a predilection site for thrombosis formation. Vortical blood flow in the sinus leads to local hypoxia, which activates the endothelium, and subsequently recruitment, activation and binding of monocytes (Mc), platelets (Plt) and tissue factor-positve microparticles (MP).

Damage to the vessel wall, and thereby the endothelium, leads to exposure of tissue factor (TF), which is the main trigger of the extrinsic pathway of the coagulation cascade (91). This cascade leads, through a complicated system with feed-forward and feedback mechanisms, ultimately to the deposition of fibrin and formation of a clot (91). Surgery, indwelling vascular catheters and trauma are well-known VTE risk factors (92). However, Sevitt reported no signs of vessel wall injury in a classic study of 50 thrombi from femoral valve pockets (93), and it seems that (mechanical) damage to the endothelium is not a pivotal factor for

VTE. Nonetheless, in the meaning of endothelial dysfunction (e.g. as described above in the valvular sinuses), this cornerstone of the triad still applies.

Blood coagulability is of great importance in the pathogenesis of venous thrombosis, illustrated by the fact that VTE is treated and prevented by anticoagulant drugs. Inherited thrombophilia, as well as a diversity of acquired prothrombotic states, represent major causes of VTE. Of the inherited thrombophilias, some (such as the factor V Leiden mutation) are prevalent in the population but give rise to only a modest relative risk increase. Others (such as antithrombin deficiency) are rare but associated with a dramatically increased risk of VTE (94). Acquired states, such as the antiphospholipid syndrome (95), heparin-induced thrombocytopenia (96) and paroxysmal nocturnal hemoglobinuria (97) may also give rise to dramatic thrombotic complications.

Obesity and arterial thrombosis

Obesity, and especially abdominal obesity, contributes to known cardiometabolic risk factors such as hypertension, dyslipidemia and hyperglycemia (98). In fact, the obesity epidemic is regarded as the main responsible for the raising prevalence of the metabolic syndrome (99). However, obesity is a predictor of CVD independent of the above mentioned risk factors (100). Inflammatory activity may be the key to this association (101). The state of chronic low-grade inflammation in adipose tissue promotes atherosclerosis (102, 103). Obese individuals also have increased platelet activation (104), and strong evidence exists that obesity is associated with alterations in the coagulation and fibrinolytic systems (105, 106). In addition, obesity induces structural changes in the heart, including left ventricular hypertrophy, diastolic dysfunction and cardiomyopathy of obesity (”adipositas cordis”) (107). Even though the association between obesity and arterial thrombosis is a complex one, its origin is quite thoroughly elucidated. Finally, treatment of obesity-related co-morbidities such as hypertension, diabetes and dyslipidemia does lead to a substantial reduction of cardiovascular risk (108).

Obesity and venous thromboembolism

The underlying pathophysiological mechanisms by which obesity increases risk of venous thrombosis remain not fully understood. The traditional cardiovascular risk factors associated with obesity have little impact on VTE risk (12, 13, 79), and the increased risk of VTE in the metabolic syndrome is essentially dependent on the presence of abdominal obesity (16, 109).

Even though the components of the metabolic syndrome apart from abdominal obesity are not directly associated with VTE risk, there is a strong relation between the syndrome and a prothrombotic state (110). Venous thrombi are not platelet-rich like arterial thrombi, but platelets still play an important role in venous thrombosis (111). In a review article Morange & Alessi summarize potential mechanisms for platelet hyperactivity associated with the metabolic syndrome, which includes increased platelet adhesiveness, aggregation and procoagulant activity, as well as increased platelet TF expression and platelet inflammation (110). Adipokines, a group of hormone-like substances derived from adipose tissue, have been suggested to be involved in the pathogenesis of obesity-related VTE (112). Both leptin and adiponectin influence TF expression in monocytes (113), but also other components involved in thrombus formation have been shown to be altered in in the presence of abdominal obesity (110). Decreased fibrinolysis, related to increased plasminogen activator inhibitor-1 (PAI-1) activity is also present in obesity (114), and leads to increased VTE risk (115, 116). In a study of obesity-disconcordant monozygotic twin pairs, Kaye and co-workers demonstrated that obesity influences the activity of fibrinogen and activities of FIX, FXI, FXII, and PAI-1 independent from genetic factors (117).

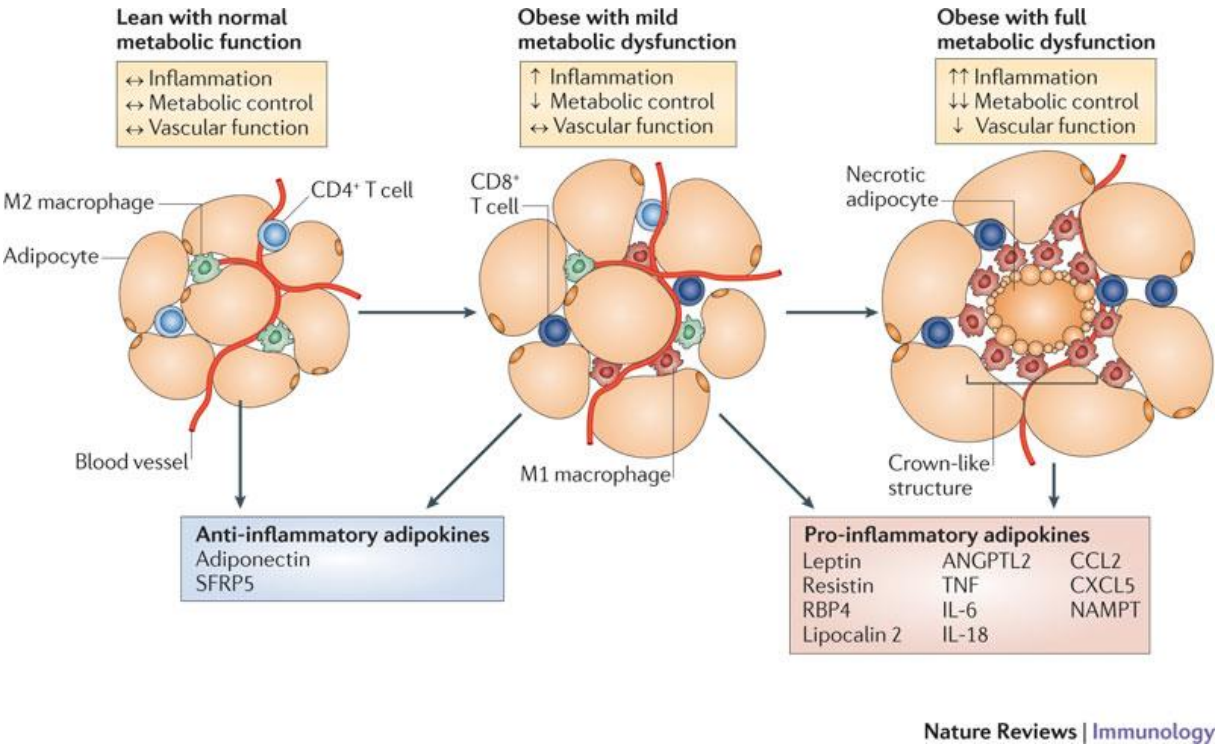

Figure 3. Obesity, adipose tissue inflammation and adipokines. Reprinted by permission from Macmillan Publishers Ltd: [Nature Reviews Immunology] (118), copyright (2011).

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The role of chronic, low-grade inflammation in VTE is unclear (119-122), but its link to coagulation abnormalities is robust (123), and adipose tissue inflammation is probably a very important "upstream" factor for a great deal of the coagulation abnormalities present in obesity (Figure 3) (102, 118).

Abdominal obesity is associated with increased intraabdominal pressure and causes hampered flow parameters in the lower limbs (124-126), which suggests that a more mechanical role of increased fat mass, causing venous stasis (Figure 4) could lead to the increased risk.

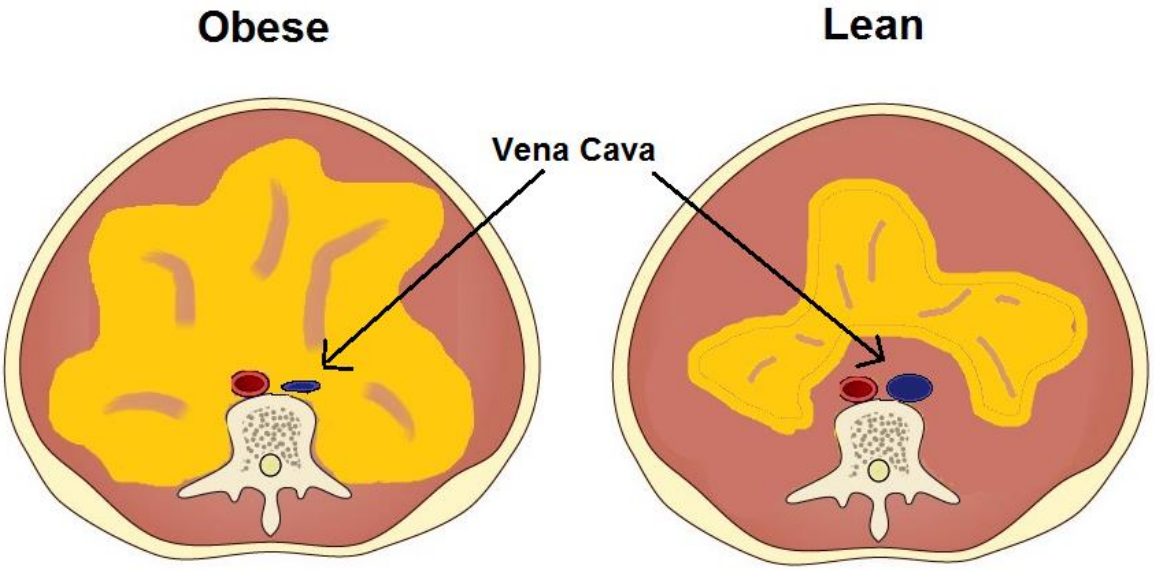

Figure 4. Increased abdominal pressure and vena cava compression due to abdominal obesity.

Results from the JUPITER trial, a randomized controlled trial of rosuvastatin with venous thrombosis as a secondary end point, showed that the incidence of VTE was significantly (43%) lower in the treatment group (127). However, Rahimi and colleagues later performed a meta-analysis of 29 trials with nearly 150 000 randomized individuals and found no or at most a very moderate protective effect of statins on venous thrombotic events (128). No study has shown a beneficial effect of antihypertensive or antidiabetic drugs on VTE risk.

Body height and venous thromboembolism

Tall subjects are at increased risk of both first (18-21) and recurrent (20, 129) venous thromboembolism. Lutsey and co-workers showed that leg length was a risk factor for VTE regardless of body height (130), which may suggest that this association is driven through alteration of venous flow parameters and venous stasis in long legs (22, 23). Taller people

also have a greater venous surface area and a larger number of venous valves, and thus a greater area where thrombi may occur (130).

Prothrombotic genotypes

Venous thromboembolism is to a large extent a genetic disease. It is estimated that the heritability of VTE is around 50 % (131-133), and the familial standardized incidence ratio (the excess relative risk of the disease from familial factors) is about 2.50 (134). The first characterization of inherited thrombophilia was the discovery of inherited antithrombin deficiency in a family from Skjervøy, Norway in 1965 (135). A cluster of venous thrombotic events had occurred in this family, and in 1964 a 12 year old boy and his mother were examined by dr Olav Egeberg at Rikshospitalet, Norway. Plasma samples from the two and additionally 15 family members were collected, and there were significantly lower activity in "progressive antithrombin" and "heparin co-factor" among the seven individuals who had experienced a thrombotic event compared to those who had not. The condition displayed an autosomal dominant inheritance pattern (135). Some years later, deficiencies of protein C (136) and protein S (137) were discovered, and it was also shown that ABO blood group influenced VTE risk (138).

During the two previous decades, a number of relatively common prothrombotic genetic risk factors have been elucidated (Table 1). In 1994, the Factor V Leiden (FVL) mutation, also known as rs6025, was discovered (139, 140), and two years later, the prothrombin gene mutation (rs1799963) was identified. Then, polymorphisms in the PROCR (rs867186) (141) and FGG (rs2066865) (142) genes followed. When genome-wide association studies became available in the 2000s, additional single nucleotide polymorphisms (SNPs) associated with VTE risk were discovered, although displaying weaker associations than previous discoveries. Recently, targeted gene sequencing, whole exome sequencing and whole genome sequencing have been available to identify extremely rare mutations causing the disease (143).

Family and twin studies have suggested that up to 60 % of VTE risk is attributable to genetic factors (131, 144). However, only approximately 5 % of VTE heritability can be accounted

for by the common genetic polymorphisms known to date (145). Thus, there is yet an unmet potential to discover the mechanisms behind this heritability, and gene-environment interactions (such as interactions between genotypes and obesity) could potentially be one.

Table 1. SNPs and Genes associated with VTE identified by GWAS (143)

Gene	Site	Phenotype	Frequency	VTE OR
F2	rs1799963	↑ FII	0.02	2.5
F5	rs6025	Resistance to activated protein C	0.05	3
FGG	rs2066865	↓ Fibrinogen γγ'	0.25	1.47
ABO	rs8176719	↑ VWF, ↑ VIII	0.3	1.5
ABO	rs2519093	Unknown	0.24	1.68
PROCR	rs867186	↑ sEPCR, ↑ PC	0.07	1.22
SLC44A2	rs2288904	Still unknown	0.79	1.19
STXBP5	rs1039084	increase vWF	0.46	1.11
VWF	rs1063856	increase VWF	0.37	1.15
KNG1	rs710446	decrease aPTT	0.45	1.2
GP6	rs1613662	increase Platelet function	0.82	1.15
TSPAN15	rs78707713	Still unknown	0.88	1.28
F11	rs2289252	increase F11	0.41	1.35
F11	rs2036914	increase F11	0.52	1.35

Interactions between obesity and other known risk factors

A risk factor is a condition, behavior or other factor that increases the risk of a disease. The population attributable risk indicates the proportion of cases that would not occur in a population if the factor was eliminated (e.g. how many VTEs would be avoided if no people were obese?). Both the prevalence of a risk factor and the strength of association between the risk factor and a certain disease affects the population attributable risk. Thus, the 2-3 fold increased risk in obese individuals has a great impact on the population, given that more than half a billion adults worldwide are obese (47).

The thrombosis potential model, as proposed by Rosendaal, describes the need of additive effects from several risk factors for thrombosis to occur (11). Individual, moderate risk factors

may not in themselves be sufficient to trigger a VTE, but if they act in an additive or even synergistic way, the sum of these result in a high "thrombosis potential" (11). Thus, in an elderly, obese subject, the addition of a subsequent risk factor such as an acute infection may be sufficient to exceed the threshold needed to trigger a thrombotic event. If the subject in question also is a carrier of a prothrombotic gene mutation, the thrombosis potential might be even higher (Figure 5).

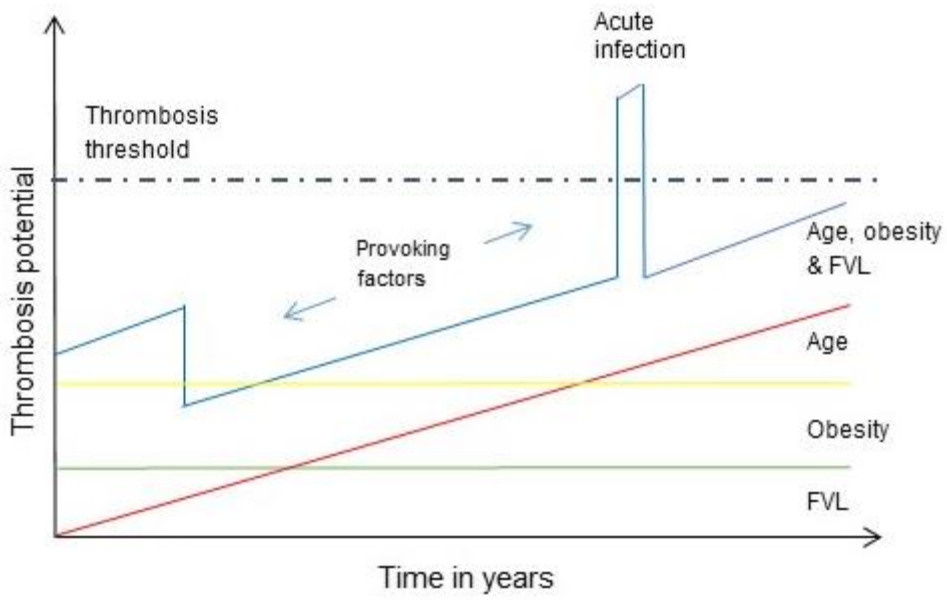

Figure 5. The thrombosis threshold model. The green line represents an intrinsic risk factor such as Factor V Leiden (FVL), the yellow line represents obesity and the brown line represents age. The blue line demonstrates the joint effect of age, obesity and FVL. The presence of additional provoking factors (such as an acute infection) even further increases the risk. This combination exceeds the thrombosis potential threshold and the individual develops a symptomatic VTE. Adapted from Rosendaal FR (11).

Interaction occurs when the combined effect of two risk factors is not additive. When this combined effect exceeds the sum of the individual components, a synergistic effect is present. To some extent, possible interactions between obesity and other prothrombotic risk factors have been studied. Taller men have an increased risk of VTE (18), and the joint effects of a tall stature and obesity were associated with a substantially increased risk in a study by Borch et al (146). Pomp and co-workers investigated the joint effects of obesity and prothrombotic mutations as well as oral contraceptive use in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. They found an 8-fold increased risk for obese carriers of the factor V Leiden mutation compared to normal-weight non-carriers, and a corresponding 7-fold increased risk for obese carriers of the prothrombin 20210A mutation (14). Synergistic or additive effects between obesity and these mutations have also been described in other, smaller studies (17, 122, 147). In the study by Pomp and co-workers, there was a 24-fold increased risk of VTE in obese women who used oral contraceptives compared to normal-weight non-users (14), and a similar combined effect was also present in a case-control study by Abdollahi et al (148).

AIMS OF THE STUDY

1. To assess and compare whether the pattern of body fat distribution, assessed by anthropometric measures (body mass index, waist circumference, hip circumference, waist-hip ratio and waist-height ratio) has a differential impact on the risk of arterial (e.g. myocardial infarction) and venous (e.g. VTE) thrombosis. Further, to explore how obesity-related atherosclerotic risk factors influence the relationship between obesity and arterial and venous thrombosis.

2. By taking repeated measurements into account, to investigate the associations between c-reactive protein (CRP) and the risks of VTE and MI, and to explore whether chronic low-grade inflammation (assessed by CRP) partly mediated the risks of these outcomes in obese subjects.

3. To investigate whether changes in body weight over time is associated with increased risk of venous thromboembolism in a population-based cohort study.

4. To investigate the combined effect of prothrombotic genotypes and tall stature on the risk of VTE.

METHODS

Study populations

The Tromsø Study is a single center prospective follow-up study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway (149). The study is conducted by the Department of Community Medicine at the University of Tromsø, and the main focus is on cardiovascular disease. The first survey was carried out in 1974, followed by surveys in 1979-80, 1986-87, 1994-95, 2000-01, and 2007-08. The fourth survey of the Tromsø Study (Tromsø IV) was conducted in 1994-95. All inhabitants aged > 24 years were invited, and a total of 27 158 subjects participated (77 % of the eligible population). All participants aged 55-74 years and 5-10 % random samples in the other 5-year birth cohorts were invited to a more extensive second screening visit, and 6 889 subjects participated (78 % of those invited). Tromsø V was conducted in 2001-02 and included 8130 subjects aged 30-89 years of age (79 % of the eligible population). Tromsø VI was conducted in 2007-08 and included 12984 subjects aged 30-87 years of age (66 % of the eligible population).

The papers included in this thesis are all based on prospective follow-up studies on subjects who participated in these surveys. Paper I includes subjects from Tromsø IV only, while paper II additionally includes subjects from Tromsø V and VI. In paper III, anthropometric measures from subjects who attended Tromsø IV were also collected from Tromsø III where available.

Subjects in paper I and II were followed from the date of enrollment in the Tromsø Study until December 31, 2010. In paper II, we used a time-varying approach, where subjects who attended multiple surveys had their exposure data updated at each survey. In paper III, only subjects who attended at least two subsequent surveys were included, and they were followed from the date of the second of two subsequent visits until the date of the next survey or December 31, 2012. Subjects who attended three or more subsequent surveys thus contributed with multiple observations with different exposure information.

For paper IV, we conducted the analyses using a case-cohort design, based on the entire Tromsø 4 and 6 cohorts. Subjects who attended at least one of these surveys were followed from the date of attendance until the date of an incident VTE, death, migration or December 31st 2012, whichever came first. All incident VTEs (n=689) during follow-up were included as cases, and a sub-cohort, consisting of 2 011 age-weighted subjects randomly selected from the entire cohorts was then sampled.

Exposure assessment

Baseline information was collected by physical examinations, blood samples, and validated self-administered questionnaires. Blood samples were collected from an antecubital vein, serum and citrated plasma prepared by centrifugation after one hour respite at room temperature, and frozen at –70 °C. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846, Critikon Inc) by trained personnel. Participants rested for 2 minutes in a sitting position, and then 3 readings were taken on the upper right arm separated by 2-minute intervals. The average of the last 2 readings was used in the analysis. Nonfasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 hour respite at room temperature and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods and commercially available kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boeringer Mannheim, Germany). Serum high density lipoprotein (HDL)-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Determination of glycosylated hemoglobin (HbA1c) in EDTA whole blood was based on an immunoturbidometric assay (UNIMATES, F. Hoffmann-La Roche AG). The HbA1c percent value was calculated from the HbA1c/Hb ratio. Hs-CRP was measured by a particle-enhanced immunoturbidimetric assay on a Modular P autoanalyzer (Roche/Hitachi) using reagents from Roche Diagnostics GmbH, Mannheim, Germany. The lower detection limit of the hs-CRP assay was 0.03 mg/L and measurements of hs-CRP lower than 0.03 mg/L were therefore set at this value. The analytical coefficient of variation for hs-CRP levels between 0.1 and 20 mg/L was less than 4 %. Information on self-reported diabetes, smoking habits, alcohol

consumption, dietary habits, family history of cardiovascular diseases and concurrent diseases was obtained from standard, validated self-administered questionnaires. Height and weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Waist circumference (WC) was measured in centimeters at the umbilical line. Hip circumference (HC) was measured in centimeters at the widest point at the hips. Waist-Hip-ratios (WHR) were calculated by dividing WC by HC. Waist-height ratios were calculated by dividing WC by height. Incident cancer diagnoses during follow-up were obtained from the Cancer Registry of Norway.

Genotyping of the SNPs rs6025 (FVL), rs1799963 (F2), rs8176719 (ABO), and rs2036914 (F11) was done using the Sequenom platform and rs2066865 (FGG) by the TaqMan platform. Sequenom uses single-base extension followed by mass spectrometry to measure the molecular mass of the extended primers. Samples were genotyped using the Sequenom iPlex Gold Assay according to the recommended protocol, using an initial input of 10-20 ng DNA and were analyzed using the MassARRAY Analyzer 4. We only used genotypes with a high quality score of "A. Conservative" or "B. Moderate". When multiple attempts were made to genotype an individual, one of the highest quality genotypes across all attempts was chosen for each SNP. For TaqMan, we used an initial input of 100 ng of DNA. Samples were genotyped using the Applied Biosystems 7900HT according to the recommended protocol, processed using SDS 2.4 (Thermo Fisher), and genotypes passing a quality value threshold of 95 were used.

Outcome measurements

Venous thromboembolism

All first lifetime events of VTE were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway from date of enrolment in the Tromsø study (1994–1995) to January 1, 2012. All hospital care and relevant diagnostic radiology in the Tromsø municipality is provided exclusively by this hospital. The relevant discharge codes were ICD-9 codes 325,

415.1, 451, 452, 453, 671.3, 671.4, 671.9 for the period 1994 to 1998 and ICD-10 codes I80.0-I80.3, I80.8, I80.9, I81, I82.0-I82.3, I82.8, I82.9, I67.6, O22.3, O22.5, O87.1, O87.3, I26.0 and I26.9 for the period 1999 to 2012. The hospital discharge diagnosis registry included diagnoses from outpatient clinic visits and hospitalizations. An additional search through the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE either as cause of death (part 1 of the death certificate) or as a significant condition (part 2 of the death certificate) were identified. We also searched the radiology database to identify cases with objectively confirmed VTE that may have been missed due to coding errors in the hospital discharge diagnosis registry. All relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during the 18-year period were systematically reviewed by trained personnel, and cases with confirmed VTE were identified.

The medical records for each VTE-case derived from the hospital discharge diagnosis registry, the autopsy registry, or the radiology procedure registry were reviewed by trained personnel. An episode of VTE was confirmed and registered as a validated VTE-event when all 4 of the following conditions were satisfied: (1) confirmed by diagnostic procedures including compression ultrasonography, venography, spiral computed tomography (spiral CT), perfusion-ventilation scan (high or moderate probability for PE), pulmonary angiography, or autopsy; (2) the medical record indicated that a physician had made a diagnosis of DVT or PE; (3) signs and symptoms consistent with DVT or PE were present, and (4) the patient underwent treatment with anticoagulants (Heparin, Warfarin), thrombolytic therapy, or vascular surgery. For patients derived from the autopsy registry a VTE-event was recorded when the autopsy record indicated PE as cause of death or as a significant condition contributing to death.

Myocardial Infarction

Adjudication of hospitalized and out-of hospital events was performed by an independent endpoint committee and based on data from hospital and out-of hospital journals, autopsy records, and death certificates. The national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of incident myocardial infarction were identified by linkage to the discharge diagnosis registry at the University Hospital of North Norway (UNN) with search for ICD 9 codes 410-414 in the period 1994-98 and thereafter ICD 10

codes I20-I25. The hospital medical records were retrieved for case validation. Modified WHO MONICA/MORGAM criteria for myocardial infarction were used and included clinical symptoms and signs, findings in electrocardiograms (ECG), values of cardiac biomarkers and autopsy reports when applicable. Further, linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal incident cases of myocardial infarction that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø, as well as information on all-cause mortality. Information from the death certificates was used to collect relevant information of the event from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners.

MAIN RESULTS

Paper I: Obesity Measures and Risk of Venous Thromboembolism and Myocardial Infarction

The aim of this study was to compare the impact of different anthropometric measures of obesity on risk of venous thromboembolism and myocardial infarction, and to explore how obesity-related atherosclerotic risk factors influenced these relationships

Obesity measures including body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR) and waist-height ratio (WHtR) were registered in 6 708 subjects aged 25 – 84 years who attended the Tromsø IV study. Information on traditional atherosclerotic risk factors (blood pressure, blood lipids, HbA1C, diabetes and smoking habits) was obtained by physical examination and questionnaires. Incident VTE and MI events were registered until December 31, 2010. During a median of 15.7 years of follow-up, there were 925 incident MI cases and 288 VTE events. All obesity measures were associated with VTE risk. In quintile-based analyses, the risk of VTE increased across higher quintiles of all obesity measures in both genders, and remained unchanged after adjustment for traditional atherosclerotic risk factors. WC yielded the highest risk estimates in men (HR upper vs. bottom quintile: 3.54, 95 % CI 1.82-7.06), while HC showed the strongest association in women (HR 2.27, 95 % CI 1.54-4.92). In comparison, all measures of obesity were associated with MI in men, but HC showed a weaker association than the other measures. Only BMI, WC and WHR were associated with VTE risk in women. The risk estimates for MI were substantially attenuated (33-68 % points) after adjustment for atherosclerotic risk factors. In conclusion, our findings imply that the impact of body fat distribution, and the causal pathway, differs for the association between obesity and arterial and venous thrombosis.

Paper II: Low-Grade Inflammation, assessed by C-Reactive Protein, Is a Mediator of Obesity-Related Venous Thromboembolism in Women

This study was undertaken to investigate whether chronic, low-grade inflammation, assessed by C-reactive protein, is a shared pathway for the association between obesity and arterial and venous thrombosis. Using repeated measures of anthropometric measures of obesity and serum levels of C-reactive protein, we used Cox-regression models to calculate hazard ratios of MI and VTE according to categories of CRP and obesity measures, and explored how adjustment for CRP affected risk estimates by obesity. There were 291 VTEs and 920 MI events during follow-up. High levels of CRP (≥3 mg/L versus <1 mg/L) were associated with increased risk of MI (HR 1.73; 95 % CI 1.32-2.26) and VTE (HR 1.84; 95 % CI 1.22-2.78) in women, but only with MI in men (HR 1.93; 95% CI 1.53-2.44). All obesity measures displayed stronger associations with CRP in women than in men. In obese women (BMI ≥30 kg/m^2 versus <25 kg/m^2), adjustment for CRP attenuated the risk estimate for VTE by 22 % whereas incidence rates of VTE increased with combined categories of higher BMI and CRP. In men, no such association was found. In contrast, CRP was associated with risk of MI in both genders, and risk estimates for MI in obesity were attenuated by 22-45 % after adjustment for CRP. In conclusion, our findings suggest that chronic low-grade inflammation may be a shared pathway for obesity-related MI and VTE, particularly in women, but the associations appear to be weaker for VTE than for MI.

Paper III: Impact of Weight Change on Risk of Venous Thromboembolism

The purpose of this study was to investigate whether changes in body weight influenced VTE risks in a general population. Subjects who attended two or more (out of four) subsequent surveys of the Tromsø study in the period of 1986 to 2007 were followed from the date of the second of two subsequent visits until the date of the next survey, December 31st 2012, the date of an incident VTE, death or migration. Subjects who attended three or more subsequent visits thus contributed with multiple exposures and observations. A total of 17 802 subjects, aged 25-89 years were included in the study. Cox-proportional regression models were used to calculate risks of VTE according to change in body weight (body weight first visit – body

weight second visit), using subjects with no or a moderate (<7.5 kg) weight gain as reference. There were 302 incident VTEs during a median follow-up of 6.0 years. Subjects who gained more than 7.5 kg had a 1.9-fold increased risk of VTE (HR 1.92; 95 % CI 1.38–2.68). The risk estimate was moderately attenuated but still statistically significant (HR 1.64; 95 % CI: 1.15-2.30) after adjustment for the attained BMI. The increased risk by weight gain was most highly pronounced among subjects who were already obese (BMI ≥30 kg/m^2) at baseline (HR 3.75; 95 % CI 1.83-7.68). Compared to normal-weight subjects with 0-7.4 kg weight gain, these subjects had a 6.6-fold increased risk of VTE (HR 6.64; 95 % CI 3.61-12.22). Further analysis revealed that the elevated risks were only present for unprovoked VTE. Risk estimates were essentially similar when taking incident cancer and competing risk by death into account. We also found a slightly increased risk of provoked VTE associated with weight loss, but this was not statistically significant. In conclusion, our findings suggest that weight gain, independent of the attained BMI, is a risk factor for VTE, and that the associated risks are particularly high among subjects who are already obese.

Paper IV: Joint effects of prothrombotic genotypes and body height on the risk of venous thromboembolism: The Tromsø Study

In this study, we sought to investigate potential synergistic effects between prothrombotic genotypes and a tall stature on VTE risk. Within a case-cohort derived from the Tromsø study, 689 subjects with incident VTE (cases) and 2011 age-weighted, randomly sampled individuals (sub-cohort) comprised the study population. We investigated whether multiple SNP testing (rs6025 (FVL), rs1799963 (F2), rs8176719 (ABO), rs2066865 (FGG) and rs2036914 (F11)) and the genetic risk score proposed by de Haan et al (150) in combination with a tall stature yielded excess risk of VTE. Age- and sex-adjusted hazard ratios (HR) of VTE were calculated by categories of risk alleles (de Haan 5-SNP score; 0-1, 2-3 and ≥4) and body height (<40^{th}, 40-80 and >80^{th} percentile).

As expected, subjects ≥178 cm (>80th percentile) had a 2-fold higher risk of VTE (HR 2.04; 95% CI 1.51-2.73) compared to those <165 cm (<40th percentile), and an increasing number of risk alleles were also associated with risk of VTE ($p<0.001$). However, in contrast to obesity, the combination of a tall stature and the presence of genetic risk factors did not yield excess risk of VTE. Subjects with body height ≥178 cm and ≥4 risk alleles only had a 2-fold (HR 2.08, 95% CI 1.24-3.52) higher VTE risk than subjects ≤165 cm with 0-1 risk alleles. In conclusion, our study suggested that no biological interaction is present between a tall stature and a genetic predisposition for VTE.

GENERAL DISCUSSION

Methodological considerations

Study design

The four papers presented in this thesis are all based on a population-based prospective cohort study. The purpose of most epidemiological studies is to identify exposures that may affect the risk of developing disease or other health-related outcomes. In a prospective cohort, a defined population is followed from inclusion until the outcome of interest or another censoring event such as death, migration or end of study period. Compared to other designs, cohort studies have several advantages. There is a clear temporal sequence between exposure and outcome, which rules out reverse causality. Further, compared to a retrospective study, a cohort is more likely to obtain valid and unbiased information on exposure status, and both absolute and relative risks may be provided (151). Our cohort comprises a large number of participants, with participation rates ranging from 66-77 % of the eligible population. This enhances the external validity and generalization of study findings to the background population.

One of the main disadvantages of the cohort design is its lack of ability to study rare diseases. When the incidence of a disease is low, a very large study population and long follow-up is required to generate results with adequate statistical power. Case-control studies are better suited to investigate rare outcomes, as they include individuals with the disease of interest and match these subjects with controls. Subsequently, information about exposure is collected among cases and controls through self-report or data from databases (151). In this way, they are both cost- and time-efficient. However, as exposure data is collected after the event of interest, the possibility of reverse causation (i.e. that the outcome is the determinant of the exposure and not vice versa) is present. Also, subjects who have experienced an event may have searched their memories more thoroughly for potential triggering factors, a phenomenon known as recall bias (151). Further, selection bias (e.g. that only the youngest and healthiest

cases agree to participate in the study, or that the controls are not representative of the reference population) is an issue of concern (151). It is crucial that the frequency of the exposure variables is representative of the reference population.

The nested case-control study (a case-control study within a cohort study) is an efficient study design, where cases who develop a disease in the cohort are matched with individuals in the cohort who where alive and had not developed the disease at the time of matching (152). Thereby, subjects who experience an event (near the end of follow-up) may also be included in the sub-cohort. In this design, exposure data is collected prior to the events of interest, eliminating the possibility of reverse causation. In paper IV, we applied a similar but less commonly used design, the case-cohort design (153) (Figure 3). All cases from the entire (parent) cohort (Tromsø 4 and 6) who developed a VTE during follow-up were included, while an age-weighted selection from the parent cohort formed a sub-cohort. Performing genotyping only within the sub-cohort is cost- and time-efficient while statistical power is retained (152). The case-cohort design has some advantages compared with a nested case-control. Firstly, it enables calculation of incidence rates based on the reference population. Furthermore, the sub-cohort can later be utilized for investigations of other end-points, such as myocardial infarction or stroke.

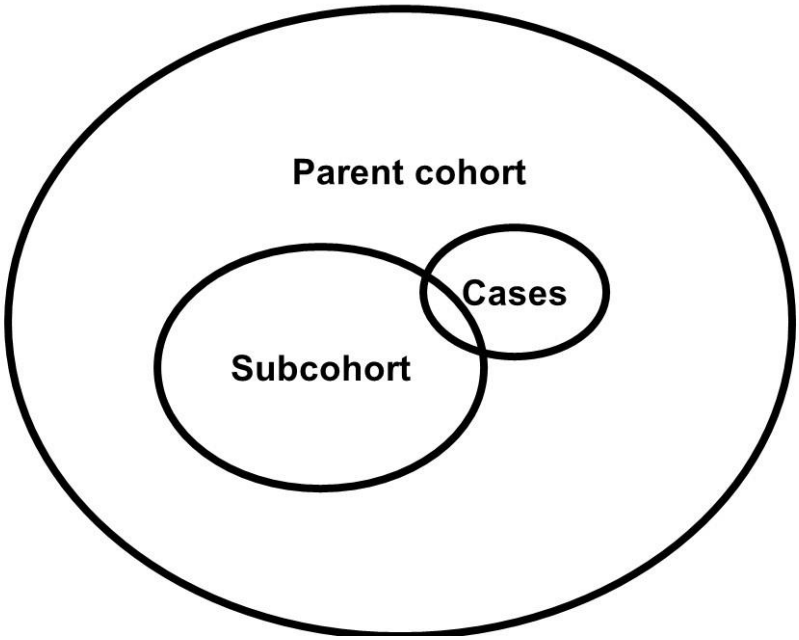

Figure 6. Case cohort design. The study included all cases who developed in the parent cohort during follow-up and age-matched controls, forming a sub-cohort. Cases occurring at a later stage of follow-up may be included in the sub-cohort, as they are event-free at the time of matching.

The randomized controlled trial (RCT) is the gold standard for establishing causality. When the participants are randomly assigned to the exposure, study populations receiving different exposures will be close to similar in every aspect, except for the intervention. Thus, the risk of confounding is greatly reduced. However, an experimental approach where participants receive a potential harmful intervention is not ethically acceptable, and this fact limits the RCT's usefulness for studying risk factors for disease. Even though the study design assures high internal validity, selected recruitment of participants (younger, healthier, more motivated) compared to the general population may limit its external validity (151). As an example, the RCT of rivaroxaban for the treatment of venous thrombosis included participants with a mean age of 56 years, while in real life the majority of VTE events occur after the age of 60 (32).

Genetic epidemiology, applying the Mendelian randomization design, is another way of potentially obtaining unbiased estimates of the effects of a causal variable without conducting an RCT. By using germline genetic variants as proxy for environmentally modifiable exposures, bias from confounding and reverse causation can be reduced (154). Some important assumptions must be met in this study design. First, the association between the genetic variant (risk allele) and the exposure of interest (intermediate factor) must be strong, and the risk allele must not be associated with other factors that may influence the intermediate factor. Further, the risk allele must act on the outcome solely via the association with the intermediate factor (154). Linkage disequilibrium (i.e. non-random association of alleles at different loci, with the consequence that Mendel´s second law cannot be applied) and population stratification (confounding by ethnicity) are also issues of concern (155). Thus, the results from this type of study design might still be confounded. Related to the work in the present thesis, Zacho and co-workers conducted a Mendelian randomization study within the prospective Copenhagen City Heart Study, where they investigated whether CRP genotypes associated with elevated plasma CRP levels were associated with risk of VTE (which it was not) (120).

Statistical analyses and interaction

In all papers presented in this thesis, Cox-proportional hazard models were applied. The first paper was based on Tromsø 4 measurements, and we used time-on-study as the time-scale. The second and third paper were based on measurements from Tromsø 4, Tromsø 5 and Tromsø 6, with age as the time-scale (156). Potential confounding factors such as age (first paper), sex (third paper) smoking, diabetes and cardiometabolic risk factors were included in adjustment models.

Due to gender-specific cut-offs for WHO risk categories of waist circumference, analyses were stratified according to sex in paper I. There is a stronger association between obesity and increased CRP in women than in men (157), therefore stratification according to sex was done in paper II as well. In the latter, the interaction term was not statistically significant when tested, and risk estimates between sexes overlapped. Still, there was a clinically significant difference in the risk estimates, and the lack of statistical significance was most probably due to limited study power. In paper III, we performed stratified analyses according to baseline

BMI (normal-weight vs overweight and obese), as well as incident cancer during follow-up. Here as well, there were no statistically significant interactions, but clinically significant differences in the risk estimates. We also applied the Fine & Gray (158) model for sensitivity analysis to account for mortality as a competing event, as weight variability is associated with increased mortality (159). Gender differences have also been reported for the association between body height and VTE, but it is plausible that this may be due to the fact that men generally are taller than women (18). There were no statistically significant interactions between sex and body height, and for power issues we chose not to present stratified analyses.

Confounding

Confounding is present when a non-causal association between an exposure and an outcome is observed as a result of the influence of a third variable (151). In other words, the confounder influences both the outcome and the exposure. Confounding is always a concern in studies dealing with causality. When present, it will result in biased estimates on the effects of the exposure on the disease. It may strengthen, weaken or even inverse the direction of the observed associations (151). In a randomized controlled trial, randomization can minimize confounding, whereas in observational studies we seek to eliminate confounding through statistical modelling, including stratification and multivariable adjustment analysis.

In the present work, several confounding factors are of importance, where the most relevant are discussed below. Firstly, age is a major confounder on most research on venous thromboembolism, as the incidence of the disease increases exponentially with age (24). Also the frequency of exposures are often strongly age-related. In Norwegian adults, body weight and BMI also tend to increase with age (160). To account for this, we applied different approaches in the different papers. In the first paper, the subjects´ age at baseline was included as a covariate in all analyses, using time-on-study as the time scale. This is perhaps the most commonly used approach in cohort studies. In the other papers, we used the subjects´ *age as the time-scale*, with the baseline age as entry-time and the age at outcome or censoring event as exit time (161). Thereby, the risk of VTE is compared in subjects with the same age instead of the same follow-up time. Hence, age is taken into account without a need for modelling its effect and a more effective control of age ensues (156). When applying the two

methods on the same data, risk estimates were overall somewhat less pronounced when using age as the time-scale.

In paper II, potential confounding might influence the relationship between obesity, CRP (which is a marker of inflammation), and VTE. Several chronic inflammatory conditions, especially cancer, give rise to both CRP (162) and increased risk of VTE (163). CRP measurements > 10 mg/L are not likely to be caused by obesity, and these observations were excluded. Further, exclusions of subjects with active or incident cancer during follow-up, as well as stratified analyses into provoked and unprovoked would be useful in this issue. Unfortunately, our study did not have the statistical power to produce acceptable precision in these sub-analyses. As chronic inflammatory conditions and cancer are related to cachexia and low body weight (164), confounding by these diseases probably would lead to an underestimation of the importance of CRP in obesity-related thrombosis.

In paper III, we addressed the impact of changes in body weight on the risk of venous thrombosis. Obesity is a well-known and important risk factor for VTE (79), and changes in body weight are more frequent among overweight and obese individuals (165). To separate the effect of the change in body weight from (the potential resulting state of) overweight or obesity, we therefore included body mass index at the second measurement as a covariate. The increased risk of VTE associated with weight loss was more unexpected. Obviously, cancer or other comorbidities could potentially cause both the weight loss and the thrombotic events. Our approach to account for this was to exclude subjects with incident cancer during follow-up and to apply the Fine & Gray model for competing risk by death (158) to account for reduced life expectancy among subjects with comorbidities. Still, risk estimates remained statistically significant. However, we cannot rule out residual confounding by co-existing conditions such as severe respiratory illnesses, or other unknown factors which we have no means of controlling for.

The fourth paper investigated possible joint effects between genetic risk factor for VTE and a tall stature on VTE risk. As the associations between genotypes and clinical outcomes are generally unrelated to environmental or behavioural exposures, the propensity for confounding is low. If the genetic risk factors also influenced body height, confounding might be an issue. However, all SNPs investigated in our study are related to the hemostatic system.

Finally, average body height as well as the allele frequencies of FVL, and probably also the other SNPs, vary across ethnic groups (166), and ethnicity may thus be a confounding factor. However, the Tromsø population comprises a relatively homogenous population except for a proportion of subjects with Sami origin (149), and it is not likely that this would influence our results substantially.

Information bias

The internal validity (the extent to which observed findings lead to correct inferences) of a study may be reduced by information bias. Misclassification arising from measurement error may be non differential (unrelated to incidence or prevalence of the outcomes) or differential (probability of misclassification differs according to incidence or prevalence of the outcomes). In cohort studies, exposure variables are usually measured prior to the development of disease, and misclassification will generally be non-differential.

In all the papers included in this thesis, information on several covariates such as smoking status, diabetes and physical activity was gathered from self-administered questionnaires. This form of collecting data is cost-efficient and valuable in large-scale cohort studies, but is a possible source of misclassification. This can be illustrated by the fact that the prevalence of self-reported diabetes mellitus in our cohort is around 1.6 %, which is lower than expected. The prevalence in Norway has previously been estimated to be around 2% (167), and our population is older and thus more prone to develop the disease. Although this misclassification probably will be non-differential, we have accounted for this by including glycosylated hemoglobin (HbA1c) measurements as a covariate in the analyses when available. In the second visit of the Tromsø 4 survey 28 out of 6 819 subjects 819 (0.4 %) had a HbA1c $\geq$ 7 % while not reporting a diabetes diagnosis, and the rates were comparable in the Tromsø 5 and 6 surveys. Moreover, both diabetes and HbA1c had a negligible impact in the statistical models. Self-reported physical activity is often overestimated in questionnaires (168) may lead to incomplete adjustment for this potential confounder, which is especially relevant in paper III. However, the Nord-Trøndelag Health Study (HUNT) applied similar questions to ours concerning physical activity. In a paper comparing results from the questionnaires with VO_2 testing on a treadmill, Kurtze and coworkers showed a strong

correlation between “vigorous” (e.g. hard) physical activity and performance on the treadmill, concluding that the questionnaire is an appropriate tool for research (169).

Anthropometric measures of obesity were recorded by study personnel. Even though the measurements of waist and hip circumference are dependent on adequate technique, both the inter- and intra-observer reliability for the anthropometric measures are high (170). Studies which make use of self-measured and self-reported measures are more prone to measurement errors, and studies in which subjects reported body weight from years back (171) are also at risk of a considerable recall bias.

In our study, blood samples were drawn in a non-fasting state. A fasting lipid profile is recommended for the assessment of cardiovascular risk (99), and this may represent another source of exposure misclassification. Still, most subjects with a Western diet spend the majority of the day in a postprandial condition, and thus non-fasting samples might actually be more accurate measurements of lipid status. Furthermore, in the Copenhagen General Population Study and the Copenhagen City Heart study, lipid levels changed at most minimally in response to normal food intake across the study population and non-fasting lipid levels predicted cardiovascular risk (172). Also in the Women`s Health Study, non-fasting HDL cholesterol, triglycerides and total/HDL cholesterol ratio predicted CVD (173), and the Emerging Risk Factor Collaboration concluded that non-fasting total and HDL cholesterol can simplify lipid assessment in vascular disease (174).

Long-term storing, freezing and thawing of blood samples may introduce bias if the stability of the biomarker is affected. The CRP samples in our study were analyzed in thawed serum aliquots, but without any freezing-thawing cycles before measurements. Tromsø 4 samples were stored at -70 ºC for 12 years, whereas Tromsø 5 and 6 samples were stored at -20 ºC and analyzed in batches for the purpose of the studies. Previous studies have shown that CRP measurements are not considerably affected by storing, freezing and thawing (175, 176).

For the genotyping of the prothrombotic risk factors, only genotypes with a high quality score of “A. Conservative” or “B. Moderate” (Sequenom platform) or a quality value threshold of 95 (TaqMan platform) were used. When multiple attempts were made to genotype an individual, one of the highest quality genotypes across all attempts was chosen for each SNP.

Modifiable risk factors, exposure misclassification and regression dilution bias

All papers in this thesis investigate modifiable risk factors, that is risk factors which are prone to changes over time. In prospective studies with long follow-up after measurements, it is likely that exposure status and risk profiles among subjects differs at study entry and end-of-study. This phenomenon, known as regression dilution bias, often leads to an underestimation of the true associations and type II errors (177). Clarke and coworkers demonstrated that in the Framingham and Whitehall studies, real associations were underestimated by one third after a decade of exposure following a single baseline survey (177).

In paper I, subjects were followed for a median of 15.7 years after a single measurement at the Tromsø 4 survey. On a population level, body weight tends to increase with age (178), and thus our risk estimates based on obesity measures are probably underestimated. However, the main focus of the paper was to compare risk estimates between arterial and venous thrombosis, and the degree of exposure misclassification bias would probably be similar for the two outcomes. In paper II, we applied a time-varying approach, where subjects who attended more than one of the three surveys had their exposure data updated at each survey (with 6-7 years intervals). Hald et al have previously investigated the impact of CRP on VTE risk, using single measurements from Tromsø 4, and found no significant associations (119). In contrast, when using CRP as a time-dependent exposure, we now found a significant, almost 2-fold increased risk. The fact that the latter paper included a substantial number of subjects from Tromsø 5 & Tromsø 6 who did not participate in the Hald et al paper would probably also influence the results.

As mentioned above, body weight is indeed a very modifiable risk factor. In paper III, we investigated how changes in body weight influenced the risk of VTE. Assuming that the potentially harmful (or beneficial) effects of changes in body weight are present at the time the actual changes are taking place, some of the effects could be missed as follow-up was initiated after the change had taken place (Fig.1). Regression dilution bias might thus be a problem. To account for this, follow-up was kept relatively short (6-7 years) and, where available, exposure status was then updated. Further, in this manner we excluded the

possibility of reverse causation, e.g. that a VTE event might be the cause of the change in body weight. Still, we do not have information on the exact variations in body weight in-between surveys. It is well-known that subjects who are overweight or obese tend to have repeated episodes of weight loss and subsequent weight gain, a phenomenon known as weight cycling (179). Thus, it is possible that subjects have lost and regained weight or vice versa between measurements.

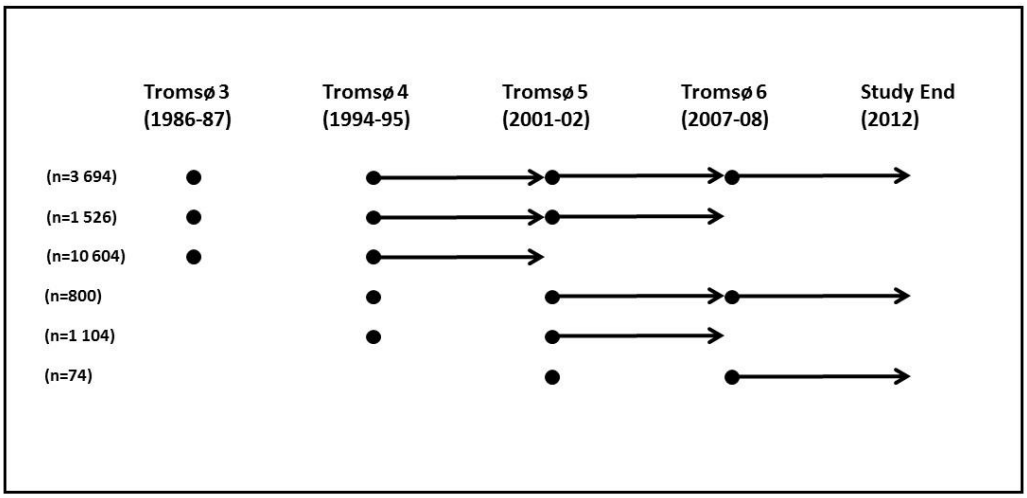

Figure 7. Overview of study participation and follow-up (paper III). Dots indicate participation at a given survey, arrows indicate follow-up. Subjects who attended two or more subsequent surveys were included, and they were followed from the second out of two subsequent visit until the date of the next survey or study end. Subjects who attended three or more subsequent surveys contributed with multiple observations with updated exposure information.

Missing data

Missing data is an issue for all epidemiological studies, and ours is no exception. There are several reasons for the missingness, including inadequate response to questionnaires,

equipment failure or loss/errors in laboratory handling of samples or other unknown reasons. Careful planning and execution of the study is critical to reduce the magnitude of missing data. A number of different approaches can be used to deal with this issue when present, but none of them are completely satisfactory. First, one can simply exclude variables with missing values (which should be done if the number of missing values for that variable is very high) or exclude subjects with missing variables (which is acceptable if the number of subjects with missing data are relatively low). Another option is imputation, where values from the available data are used to calculate an estimate replacement of the missing value.

Missing data can introduce bias, and the greatest concern is when the data is "missing not at random", meaning that the missingness is related to the variable in question. For instance, physically inactive subjects may chose not to answer questions about physical activity. Further, omitting subjects from the analyses may weaken the study`s statistical power.

In the present studies, subjects with missing values were quite similar to the subjects included in analyses with regard to clinically relevant parameters, and we chose to perform analyses on available cases (excluding subjects only from those analyses where there is a missing value in the relevant Cox regression model). For the exposure variables, there were very low percentages of missing values, ranging from <0.25 % for BMI to 1.8 % for CRP.

Outcome registration and validation

All incident symptomatic VTE events during follow-up were registered retrospectively, by using the hospital the discharge diagnosis registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway. The hospital is the exclusive provider of specialized health care in the region, with no other hospitals in a >200 km radius. All potential VTE events were thoroughly validated to avoid false positive outcomes. A VTE event had to fulfill four criteria: signs and symptoms were present, the diagnosis was objectively confirmed, a physician had made the diagnosis of deep vein thrombosis/pulmonary embolism and treatment was initiated. For cases derived from the autopsy registry, the VTE had to be noted as a cause of death or as a significant condition. Thus, the probability of a near complete VTE registry is high.

Despite the efforts made to ascertain a valid outcome registration, we cannot exclude the possibility that some VTE events were missed or misclassified. Retrospective registration is dependent on reliable and complete information, and insufficient information in medical records could lead to inaccuracy. Pulmonary embolisms sometimes present as sudden death (180), and as autopsy rates in Norway are declining (181), those events, especially when occurring out-of-hospital, were prone to misclassification. Further, it is possible that some VTE cases (e.g. in nursing homes) might have been treated on clinical suspicion without a confirmed diagnosis, or that subjects were diagnosed in another hospital while on travel. The latter cases would still most likely have been registered in the hospital diagnosis registry at follow-up consultations at the outpatient clinic.

Incident myocardial infarctions were registered retrospectively as well, with validation by qualified personnel adhering to a strict classification protocol. In addition, events observed at other hospitals were available, but they only corresponded to a small proportion of cases (<5 %).

For both myocardial infarction and VTE, diagnostic procedures and criteria have changed dramatically since the start of the study. The introduction of more sensitive diagnostic tools, such as computed tomography (CT) for pulmonary embolism and biomarkers (troponins and/or CK-MB) for myocardial infarction, have probably resulted in a relatively higher detection rate of the diseases towards the end of the study period. As the personnel who recorded the outcomes were blinded to the exposures, any misclassification was most likely non-differential, which would lead to an underestimation of the true outcome-exposure association.

DISCUSSION OF MAIN RESULTS

Body fat distribution and risk of Venous Thromboembolism (Paper I)

In paper I, we reported that all measures of obesity, including HC, were associated with increased risk of VTE. In linear models, WC was the strongest predictor for both genders, while HC showed the strongest associations in quintile-based models among women. This is in accordance with previous findings from the Danish Diet, Cancer and Health study, where more than 57 000 subjects were followed for 10 years (15). They reported that both central (i. e. large WC) and peripheral (i.e. large HC) obesity was associated with VTE risk, but with clear gender differences for the strength of associations for HC. Similar results were also present in the Iowa Women`s Health Study (21).

In contrast to VTE, we found that the measures reflecting abdominal fatness were most strongly associated with myocardial infarction, with no or much weaker associations between HC and MI. The importance of central, or visceral, adiposity on MI risk is well-known. The INTERHEART study, a case-control study comprising more than 27 000 subjects from 52 countries established WHR as the anthropometric measure most strongly associated with MI (50), and while there is some debate whether weight-to-height ratio might be even more accurate (52, 182), it is clear that it is "the waist that matters". In fact, some prospective studies have even shown that increasing HC might be protective of cardiovascular disease, at least in women (183, 184). This is in accordance with our findings, where women in the upper HC quintiles had a (non-significant) reduced risk of MI in the multivariate models. Subcutaneous adipose tissue, particularly in the gluteofemoral area, assessed by CT, magnetic resonance imaging or dual-energy x-ray absorptiometry has in several cross-sectional studies been correlated with favorable glucose and lipid levels (185-187). Further, independent of high abdominal fat, low subcutaneous thigh fat was in a study by Snijder et al related to unfavorable levels of cardiometabolic risk factors (188). It has been suggested that this protective effect is mediated by the gluteofemoral fat`s ability to entrap excess fatty acids from the circulation, and thereby prohibiting deposition of ectopic fat (189). A low HC may also reflect gluteofemoral muscle atrophy, which is associated with low insulin clearance

from muscle (190) and an impaired ability of muscle to use fatty acids (191) . However, the associations may also be confounded by factors such as an unhealthy lifestyle with physical inactivity or chronic inflammatory disease.

The reasons why we found opposite associations for HC with arterial and venous thrombosis cannot easily be explained. The aforementioned effects on insulin resistance and fatty acids probably have little impact on venous thrombosis. Abdominal obesity is associated with altered flow parameters in the lower limbs (125, 126), which may in part be explained by compression of the vena cava by increased intraabdominal pressure. No study has until date specifically investigated the influence of gluteofemoral fat on venous stasis, but it is very plausible that excess fat mass in the legs also might compress veins in the lower extremities. Unfortunately, we did not have the statistical power to investigate whether abdominal and peripheral obesity had a differential impact on the risk of proximal and distal DVT, as we would expect the mechanical effects of peripheral obesity to cause more distal thrombi. Lastly, as there is a relatively strong correlation between HC and other measures of obesity, the observed effects might also be dependent on the coexistence of abdominal fatness and the lack of a protective effect of a higher HC on VTE risk.

Impact of cardiometabolic risk factors on Venous Thromboembolism (Paper I)

In paper I, we reported that adjustment for hypertension, dyslipidemia, diabetes and Hba1c levels did not substantially attenuate risk estimates for VTE in obesity. In contrast, the risk estimates for MI were considerably reduced and by these adjustments no longer statistically significant. After the relationship between arterial and venous thrombosis became an area of attention more than fifteen years ago, several studies have investigated the association between the metabolic syndrome and risk of VTE. In a case-control study by Ageno et al. subjects referred with suspicion of VTE had a 1.9-fold higher probability of being affected by the condition if the metabolic syndrome was present (192). However, of the individual components in the syndrome, only waist circumference and triglycerides were independently associated with risk of DVT (192). In another case-control study by Ay et al, there was a (borderline significant) 2.2-fold increased risk for recurrent VTE compared to healthy

controls (193). A Korean case-control study also reported a 1.5-fold increased risk with the metabolic syndrome (194). However, results from (the few) prospective cohort studies conducted in this field have consistently shown that only obesity matters. A previous report from the Tromsø Study demonstrated that the apparent increased risk of VTE associated with the metabolic syndrome was essentially dependent on abdominal fatness alone (109). Also in the LITE study, abdominal obesity was the only predictor of VTE among the components of the syndrome (16).

Studies looking into the relationship between the traditional cardiovascular risk factors and VTE have not reported coherent findings. Among the prospective cohort studies, obesity is the only one of these risk factors that has been consistently associated with VTE. Hypertension was a predictor for VTE in the Nurses` Health Study (81) and the Copenhagen City Heart Study (195), while there was a relationship between diabetes and VTE in the LITE study (12). In the Physicians` Health Study (80) and the Tromsø Study (79), no associations were found for other factors than obesity. Family history of myocardial infarction is, together with advancing age and obesity, one of the few shared risk factors for arterial and venous thrombosis (196-198). However, this association was not explained by atherosclerotic risk factors as reported by Lind et al. (199).

Based on the existing literature and the present findings from our study, we conclude that the cardiometabolic consequences of obesity have little importance for VTE risk, and that they do not mediate the increased risk of VTE in obese individuals. Thus, unlike for MI, treatment with antihypertensive and lipid-lowering drugs will presumably not be effective in VTE prevention. The (suggested) beneficial effect of statins on VTE risk is probably mediated by other mechanisms than reduction in blood lipids (200).

Chronic low-grade inflammation and risk of VTE (paper II)

In paper II, we reported that chronic low-grade inflammation, assessed by CRP, mediated part of the association between obesity and VTE in women, but not in men. CRP was a predictor of VTE in both normal-weight and obese women. In contrast, CRP was associated with MI in

both genders, and it also mediated the associations between obesity and MI (to a larger degree than for VTE) in both genders.

The association between (central) obesity and inflammation is well studied. In the Third National Health and Nutrition Examination Survey in the United States, higher BMI was associated with higher CRP concentrations (201). In accordance with our findings, obese women had a relatively higher odds ratio (OR 6.21; 95 % CI: 4.94-7.81) for having elevated CRP levels than obese men (OR 2.13; 95 % CI 1.56-2.91), when compared to non-obese subjects. Also, a high waist-hip ratio was associated with increased CRP independently of BMI status, illustrating the higher impact of central obesity to the state of chronic inflammation (201). Further, in a meta-analysis by Choi et al., comprising 51 cross-sectional studies, the Pearson correlation (*r*) for BMI and ln(CRP) was greater in women than in men (202). It has been suggested that the sex differences in CRP may reflect differences in the inflammatory responses to obesity, and may in part be explained by differences in leptin levels (203, 204).

The first papers describing CRP as a marker of cardiovascular risk, were based on the Physician`s Health Study (205) and the Women`s Health Study (206, 207) and thus gender differences were not easily discovered. However, later studies including both sexes have shown gender differences, although in somewhat different directions. In a German study, CRP was predictive of cardiovascular disease only in women (208), while in a later meta-analysis the use of CRP improved cardiovascular risk discrimination in men only (209).

Previous studies have shown diverging results concerning the role of CRP as a VTE predictor. Several prospective studies, of which most with long follow-up, have reported no associations between CRP and VTE (119, 121, 205, 210). Regression dilution due to intra-individual variation in exposure might lead to bias towards the null. Indeed, in the HUNT study, CRP was significantly associated with CRP during the first three years of follow-up only (197). Likewise, the REGARDS study, with a follow-up of 4.6 years, showed significant associations between CRP and VTE (211). To our knowledge, no previous study has applied a time-varying approach with repeated measurements of exposure. In accordance with our findings, the REGARDS study reported a mediator effect of CRP for the association between obesity and VTE, but no gender differences were reported in the paper (211).

In sum, our findings suggest that chronic low-grade inflammation is a moderate risk factor for VTE, and that it does mediate part of the association between obesity and VTE, at least in women.

Changes in body weight and risk of VTE (paper III)

We found that weight gain was a risk factor for VTE, and that the risk was still significantly elevated independent of the resulting BMI. The risks were especially pronounced for subjects who were already obese at baseline, suggesting a synergistic effect of obesity and weight gain. Further, the risks associated with weight gain were higher for unprovoked than provoked VTE events. In contrast, there was a slightly increased risk of provoked VTE associated with weight loss among subjects with baseline BMI ≥25 kg/m^2, although this was not statistically significant. Surprisingly, the latter association was stronger when subjects with incident cancer during follow-up were excluded. However, when the competing risk of death was taken into account, risk estimates were slightly attenuated and residual confounding by concomitant illnesses (such as respiratory diseases is not unlikely. While our study is the first to examine the effect of changes in body weight on the risk of VTE, several studies have assessed the risk of cardiovascular disease, diabetes and mortality related to weight changes.

Lissner and co-workers used data from the Framingham Heart Study to investigate whether variability in body weight from age 25 (recalled weight) through eight biennial follow-up examinations was related to overall mortality, cardiovascular mortality and cardiovascular morbidity. Subjects with highly variable body weight were at increased risk for all end-points, also in models adjusted for obesity and trends in weight and cardiovascular disease (212). Other cohort studies have also shown that fluctuations in body weight are associated with increased risk of coronary heart disease (213-215).

In the Nurses` Health Study, weight gain after 18 years of age did increase the risk of coronary heart disease, also for women within the normal BMI range of 18 to 25 kg/m^2 (171). It also increased the risk of hypertension (216). Furthermore, a modest weight gain increased the risk of diabetes mellitus two-fold (217). This study relies on retrospective self-report of

body weight at age 18, which could be a substantial source of misclassification bias. In a cohort of British middle-aged men, weight gain increased the risk of myocardial infarction, while weight loss did not give rise to the expected risk reduction (218). Similar results were also found in a study of Swedish men (219).

The epidemiological evidence from these studies indicates that weight gain during adulthood is harmful, and our study suggests that this also is true for venous thrombosis. However, the lack of protective, or even harmful, effect of weight loss must be interpreted with caution, as the reasons for weight loss are not well-described. As there is a linear relationship between obesity and VTE risk, we would expect a beneficial effect of weight loss among obese individuals. Weight loss does lead to a reductions of pro-thrombotic parameters in blood (220-224). However, as there are 6-7 year intervals between visits in the Tromsø study, we do not have accurate information of changes in body weight in between the surveys. A large proportion of the adult population are at any given time trying to reduce their body weight, but unfortunately, the weight loss obtained by dieting is often rapidly regained (225). As described by Montani et al, weight cycling may contribute to "repeated overshoots" of cardiovascular risk factors during the weight regain phase (165). It is likely that also the risk of VTE is increased in this period, although this has not been investigated. Thus, a proportion of subjects registered with weight loss in our study could in reality be "weight cyclers". However, there was no clustering of cardiometabolic risk factors among subjects who lost weight.

In conclusion, our findings suggest that similarly that for cardiovascular disease, weight gain is a risk factor for VTE independent from obesity.

Prothrombotic genotypes, body height and VTE (Paper IV)

In paper IV, we assessed the combined effect of prothrombotic genotypes and body height on VTE risk. Increasing body height and number of prothrombotic risk alleles were both associated with risk of incident VTE when investigated separately, but the combination of a tall stature and the presence of prothrombotic genotypes did not yield excess risk.

The association between a tall stature and VTE risk has been described in several studies (18, 20, 21), although some previous reports only found significant associations in men. This can probably be attributed to the fact that men generally are taller than women, and only few women grow sufficiently tall to be at elevated risk. In our study, there was no statistical interaction for sex, and we therefore chose not to stratify for this variable.

Although not thoroughly investigated, the proposed mechanisms linking a tall stature to venous thrombosis involves longer legs, a greater number of venous valves and a greater venous surface area. No evidence suggest that body height influences the hemostatic or fibrinolytic systems. In contrast, obesity does promote a hypercoaguable state involving both platelets (110), coagulation (112, 117, 226) and fibrinolysis (105), giving substrate for a biological interaction with genetic variants causing alterations in these systems. Several studies have reported excess risk associated with the combination of obesity and genetic risk factors for VTE (14, 17, 122, 227). Given that a tall stature does not provide a substrate for biological interactions, it is not very surprising that we found no synergistic effect for the presence of genetic prothrombotic risk factors and a tall stature on VTE risk.

CONCLUSIONS

- In our study, body fat distribution had a differential impact on the risk of MI and VTE. Central obesity, assessed by WC, was associated with both outcomes, whereas peripheral obesity (assessed by HC) only led to an increased risk of VTE. Obesity-related atherosclerotic risk factors did not influence the risk of VTE among obese subjects, whereas adjustment for these factors substantially attenuated the risk estimates for MI in obese subjects.

- Chronic, low-grade inflammation appeared to be a shared pathophysiological pathway for the association between obesity and arterial and venous thrombosis, at least in women. However, it explained only a small fraction of the increased risk of VTE in obesity.

- Changes in body weight were associated with risk of VTE. Weight gain, independent from the attained BMI, was associated with a significantly increased risk of VTE. The risks were highest among subjects who were already obese, and there was a synergistic effect of weight gain and obesity on VTE risk.

- Increasing body height and number of pro-thrombotic risk alleles were both associated with VTE risk when investigated separately. However, the combination of these exposures did not yield excess risk, suggesting that there is no biological interaction between a tall stature and a genetic predisposition for VTE.

FINAL REMARKS AND FUTURE PERSPECTIVES

Given the still increasing prevalence of obesity world-wide, obesity-related VTE represents a major global health burden. Based on the literature and the findings of the present thesis, the mechanisms by which obesity causes venous and arterial thrombosis probably differ. Primary prevention, including treatment of hypertension and dyslipidemia, have led to a substantial decrease in the incidence of acute coronary heart disease (228). In contrast, the incidence of venous thrombosis is increasing (24) and primary prophylaxis for VTE is restricted to anticoagulation therapy in selected, high-risk (cancer) patients. To be able to prevent and design targeted treatment for obesity-related VTE, further insights into the underlying pathophysiological mechanisms are needed.

We are currently investigating the role of adipokines in obesity-related thrombosis within the Tromsø Study framework. We are also conducting experimental research on adipose tissue inflammation in cell cultures. Given the unexpected slightly increased risk of VTE associated with weight loss in the present study, investigations into VTE risk within clinical trials of weight loss programs would be of great interest. Furthermore, more studies are warranted to explore venous hemodynamics in obese subjects and the associated VTE risk.

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