Cardiovascular risk factors, atherosclerosis and venous thromboembolism - The Tromsø study

Erin Mathiesen Hald
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Faculty of Health Sciences, Department of Clinical Medicine

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SUMMARY

Venous thromboembolism (VTE) is a collective term for pulmonary embolism and deep vein thrombosis. While common and potentially fatal, VTE frequently occurs in the absence of obvious predisposing factors. Recent observational studies in selected populations have suggested a closer association between arterial thrombosis (myocardial infarction (MI) and stroke) and VTE, two disease entities considered separate in terms of pathophysiology, epidemiology and treatments. The aim of this thesis was to investigate the relation between atherosclerosis, atherosclerotic risk factors and risk of incident VTE in a general population.

Our study participants were recruited from the fourth survey of the Tromsø study, conducted in 1994-95. In this study, more than 27,000 men and women, aged 25-97 years, participated, and a subset of participants (n= 9056) were also invited to a more extensive second visit. Incident VTE events were registered from the date of inclusion until the end of follow up, and in papers 1 and 4, incident MI events were also registered. Furthermore, we performed a case-control study in which 20 participants with a previous history of unprovoked VTE and 20 healthy controls were subjected to a fat-tolerance test in order to examine the potential impact of postprandial lipemia on VTE risk.

Using a cause-specific hazards approach, we found that increasing age and obesity were shared risk factors for both MI and VTE. Traditional cardiovascular risk factors, such as male gender, diabetes, current smoking, higher levels of blood pressure, triglycerides and total cholesterol, and lower levels of HDL-cholesterol, were associated with increased risk of MI, but not with VTE. Carotid atherosclerosis, as measured by intima-media thickness and total plaque area, did also increase MI risk, while no association was found between the carotid atherosclerosis measures and risk of future VTE. Increasing levels of high-sensitivity C-reactive protein (hs-CRP) did not increase VTE risk. Our null findings for hs-CRP were consistent regardless of whether hs-CRP was examined as a continuous variable or in categories. Finally, subjects with a history of unprovoked VTE had similar lipoprotein subclasses size, distribution, and postprandial lipemia as healthy controls.

Based on our present findings, atherosclerosis and atherosclerotic risk factors do not appear to be individually associated with VTE risk. The observed association between arterial and venous thrombosis may be explained by other common risk factors or restricted to the events themselves.
VE

Sammendrag

Venøs tromboembolisme (VTE) er et samlebegrep for lungeemboli og dyp venetrombose. Selv om VTE er en vanlig og potensielt dødelig sykdom, opptrer en stor andel av VTE-hendelsene uten kjente risikofaktorer eller åpenbare utløsende årsaker. For å optimalisere risikostratifisering og forebyggende tiltak er det derfor viktig å identifisere nye risikofaktorer. Data fra nyere observasjonsstudier i selektive studiepopulasjoner har antydet en nærmere sammenheng mellom arteriell trombose (hjerteinfarkt og slag) og VTE, to tilstander som vanligvis oppfattes som helt adskilte med tanke på patofysiologi, epidemiologi og behandling. Målet med denne avhandlingen var å undersøke sammenhengen mellom aterosklerose, aterosklerotiske risikofaktorer og risiko for VTE i en generell befolkning.

Studiepopulasjonen vår ble rekruttert fra den fjerde Tromsø-undersøkelsen, som ble gjennomført i 1994-95. I denne studien deltok mer enn 27 000 men og kvinner i alderen 25 til 97 år, og en undergruppe av deltagere (n=9056) ble også invitert til en mer omfattende spesialundersøkelse. Førstegangs VTE-hendelser ble registrert fra inklusjonsdato og ut oppfølgingstida, og for to artikler (1 og 4) ble også førstegangs hjerteinfarkt registrert. Vi utførte også en case-control studie hvor 20 deltagere med tidligere uprovosert VTE og 20 friske kontroller fra den sjette Tromsøundersøkelsen gjennomgikk en fettbelastningstest, slik at vi kunne undersøke hvordan postprandiale fettnivå i blodet påvirker VTE-risiko.

I en årsaksesspesifikk risikomodell fant vi at økende alder og overvekt var risikofaktorer for både hjerteinfarkt og VTE. Tradisjonelle kardiovaskulære risikofaktorer som mannlig kjønn, diabetes, røyking, høyt blodtrykk, høy nivå av triglyserider og total-kolesterol, samt lavere nivå av HDL-kolesterol, var assosiert med økt risiko for hjerteinfarkt, men ikke for VTE. Aterosklerose i halsarteriene, målt som intima-media tykkelse og totalt plakkareal, økte også infarktrisikoen, men påvirket ikke risikoen for VTE. Økende nivå av høy-sensitivt C-reaktivt protein (hs-CRP) ga ikke økt VTE risiko. Dette var tilfelle uavhengig av om hs-CRP ble undersøkt som en kontinuerlig eller kategorisk variabel. Videre hadde personer med tidligere uprovosert VTE samme størrelse og distribusjon av undergrupper lipoproteiner, samt samme postprandiale lipemi som friske kontroller.

Basert på våre funn synes ikke aterosklerose og aterosklerotiske risikofaktorer å være uavhengig assosiert med risiko for VTE. Den observerte assosiasjonen mellom arteriell og venøs trombose kan skyldes andre delte risikofaktorer eller være begrenset til manifest sykdom.
LIST OF PAPERS

The thesis is based on the following papers:

   Brækkan SK, Hald EM, Mathiesen EB, Njølstad I, Wilsgaard T, Rosendaal FR, Hansen JB.

2. Postprandial lipemia is not increased in patients with previous unprovoked venous thromboembolism.
   Hald EM, Brækkan SK, Vik A, Brodin EE, Hansen JB.

3. High-sensitivity C-reactive protein is not a risk factor for venous thromboembolism: the Tromsø study.
   Hald EM, Brækkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Brox J, Hansen JB.

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ABBREVIATIONS

AHA: American Heart Association
Apo: Apolipoprotein
ARIC-study: Atherosclerosis Risk in Communities Study
ASA: Acetylsalicylic acid
BMI: Body mass index
CCA: Common carotid artery
CHS: Cardiovascular Health Study
CI: Confidence interval
CM: Chylomicron
CRP: C-reactive protein
CT: Computed tomography
CVD: Cardiovascular disease
COC: Combined oral contraceptive
DOAC: Direct oral anticoagulant
DVT: Deep vein thrombosis
EDTA: Ethylenediaminetetraacetic acid
FVII: Factor VII
FVIII: Factor VIII
FW: Far wall
FX: Factor X
GWAS: Genome-wide association studies
HbA1c: Glycosylated hemoglobin (hemoglobin A1c)
HDL: High density lipoprotein
HL: Hepatic lipase
HMG-COA: 3-hydroxy-3-methylglutaryl coenzyme-A
HR: Hazard ratio
HRT: Hormone replacement therapy
hs-CRP: High-sensitivity C-reactive protein
HUNT: Helseundersøkelsen i Nord-Trøndelag (The Nord-Trøndelag Health Study)
ICA: Internal carotid artery
ICD: International Classification of Diseases
IL: Interleukin
IMT: Intima-media thickness
IU: International units
JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluation Rosuvastatin
LDL: Low-density lipoprotein
LITE-study: Longitudinal Investigation of Thromboembolism Etiology Study
LMWH: Low molecular weight heparin
LPL: Lipoprotein lipase
MEGA-study: Multiple Environmental and Genetic Assessment Study
MI: Myocardial infarction
NMR: Nuclear magnetic resonance
NW: Near wall
OR: Odds ratio
PAI-1: Plasminogen activator inhibitor-1
PE: Pulmonary embolism
PREVEND: Prevention of REnal and Vascular ENd stage Disease Study
PTS: Post-thrombotic syndrome
RCT: Randomized controlled trial
RPM: Revolutions per minute
RR: Relative risk
SD: Standard deviation
Sf: Swedberg flotation
TF: Tissue factor
TNF-alpha: Tumor necrosis factor alpha
TPA: Total plaque area
VKA: Vitamin K antagonist
VLDL: Very low density lipoprotein
VTE: Venous thromboembolism
vWF: Von Willebrand factor
WHO: World Health Organization
1. INTRODUCTION

“…the legs become extremely red, hot, soft and swollen…indescribable burning sensation…”
(Sushruta Samhita, Indian Ayurveda medical texts, 600-900 BC)

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 thrombus in the deep veins, most commonly in the large veins of the lower extremities, that causes complete or partial obstruction of the vessel, impairing venous return. Pulmonary embolism primarily occurs as a DVT complication, when an embolus dislodges from the original thrombosis site and passes through the right side of the heart to the pulmonary vasculature, obstructing arterial blood flow. Without preexisting heart or lung disease, the hemodynamic disturbance of PE correlates with the extent of obstruction of the pulmonary circulation, so the clinical presentation is variable, ranging from being asymptomatic to full circulatory collapse and shock.¹ Classical PE symptoms include dyspnea, tachypnea, pleuritic chest pain, coughing and dizziness, while a DVT causes symptoms such as pain, edema, increased temperature and discoloration of the affected extremity. VTE is treated with anticoagulants. Standard treatment has until recently consisted of an initial phase of concomitant low molecular weight heparin (LMWH) and vitamin K antagonist (VKA) administration, followed by VKA in monotherapy for the long-term treatment.² Recent Norwegian guidelines have implemented the use of direct oral anticoagulants (DOACs) in the standard management of VTE.³

1.1 Pathophysiology of venous thromboembolism

The traditional understanding of VTE pathophysiology is based on a triad of physiological alterations that contribute to thrombus formation and propagation, attributed to the noted 19th century German pathologist Rudolf Virchow. In his 1856 publication, he postulated three major contributors to thrombosis formation, namely changes of blood composition (hypercoagulability), alterations of blood flow (stasis) and changes in the vessel walls (Figure 1).⁴ Alterations in one or more of these components influences an individual’s propensity for VTE development.

Changes in the blood composition are important in VTE thrombogenesis. A hypercoagulable state may be acquired or inherited, caused by increased procoagulant proteins, decreased anticoagulant proteins, decreased fibrinolysis and/or the presence of variant clotting proteins that are more procoagulant.⁵ For instance, inherited deficiency of
antithrombin, a potent inhibitor of the intrinsic coagulation pathway, increases VTE-risk 10-fold. Acquired hypercoagulability can be exemplified by pregnancy, which produces a hormone-induced increase in coagulation factors FVII, FVIII, FX, fibrinogen, von Willebrand factor (vWF) and plasminogen activator inhibitor -1 (PAI-1) that persists up to 8 weeks postpartum.

Most non-traumatic venous thrombi originate in the deep recess of the venous valve sinuses of the calf veins. This finding is supported by the direct correlation between DVT frequency and the number of valves in individuals. Situations of prolonged stasis, such as immobilization and long-haul travel, render the venous valve sinus prone to thrombus formation. Experimental studies have shown irregular, vortical blood flow patterns in valve sinuses, allowing the accumulation of prothrombotic substances that are normally washed downstream. Furthermore, stasis also leads to rapid development of localized hypoxia, inducing procoagulant responses in the endothelial cells lining the valve sinus.

In arterial cardiovascular disease, vessel wall injury is usually a prerequisite for thrombus formation, with the rupture of an atherosclerotic plaque exposing subendothelial tissue factor (TF), collagen and vWF to the bloodstream as the initiating event. In contrast, the role of vessel wall injury in venous thrombosis is less certain. In a classic autopsy study, Sevitt et al found intact vascular intima in 49 of 50 lower extremity thrombi, suggesting that overt damage to the endothelium may not contribute significantly to VTE formation. Interestingly, the fibrin-rich regions attached the thrombi to the vessel wall, and not the platelet-rich regions, suggesting that activation of the coagulation system precedes platelet activation and aggregation during the formation of venous thrombi. Experimental studies have found induced vessel wall trauma to be a poor stimulus for fibrin formation. Nevertheless, injury to the venous vessel wall caused by surgery, trauma and the use of intravenous catheters is known to increase VTE risk.
The endothelial cells of veins are normally resistant to thrombosis due to the expression of various anticoagulants, such as TF pathway inhibitor, thrombomodulin, heparin-like proteoglycans and endothelial protein C receptor. Both stasis-associated hypoxia and vessel wall damage may activate the venous endothelium. Activated endothelial cells release granules called Weibel-Palade bodies, containing vWF and membrane-bound P-selectin, leading to the recruitment of leucocytes, platelets and tissue factor bearing microparticles. In turn, TF from bound monocytes and microparticles may induce thrombosis.

Figure 2. The venous valvular sinus as a predilection site for DVT initiation. The vortical flow pattern at the venous valvular sinus leads to a steep decline in oxygen tension. The resultant hypoxia activates the venous endothelium, leading to the recruitment and binding of monocytes (Mc), platelets (Plt) and TF-positive microparticles (MP). Consequently, TF from activated monocytes and microparticles may activate the coagulation cascade and initiate thrombosis formation.

**1.2 Epidemiology of venous thromboembolism**

Venous thromboembolism is a major and common health problem, affecting 1-2 per 1000 individuals each year. The incidence of first-time VTE increases exponentially with age, from a negligible rate (<5 per 100,000 per year) among children under 15 years to approximately 5 per 1000 (0.5% per year) in individuals over the age of 80. While the
incidence of DVT is reported to be approximately twice that of PE, the two conditions are commonly regarded as different clinical manifestations of the same disease. Among patients with acute DVT, clinically silent PE is found in approximately 30%, and conversely, about 60% of PE patients have concurrent DVT. Probable de novo pulmonary embolism is also described in the literature, possibly of cardiac origin or in relation to trauma.

VTE is associated with significant morbidity and mortality. Pulmonary embolism is the most common cause of vascular death after myocardial infarction and stroke, and the leading preventable cause of death in hospitalized patients. In approximately 25% of PE patients, the initial clinical presentation is sudden death, and overall mortality after a VTE event remains significantly increased up to eight years after the thrombotic event. Also, while the vast majority of VTE patients survive the initial event, the overall risk of recurrence is high, with approximately 30% of patients experiencing a recurrent event within the next 10 years following VTE diagnosis.

Other long-term complications after VTE include chronic thromboembolic pulmonary hypertension after a PE, and the development of the post-thrombotic syndrome (PTS) after a DVT. Chronic thromboembolic pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg that persists 6 months after diagnosis of pulmonary embolism. Approximately 2-4% of PE patients suffer from the condition, which results in disabling dyspnea, and shortens life expectancy due to progressive right ventricular failure. Symptoms of PTS include chronic pain, edema, erythema, varicosities, paresthesias, and in severe cases, venous ulceration in the affected leg. Even with adequate treatment, 20-50% of DVT patients subsequently develop PTS, leading to a reduction in quality of life comparable to that of patients with congestive heart failure or cancer.

Despite ongoing efforts to improve the identification and treatment of VTE events, the VTE incidence rate has not decreased in the last 25 years, and a recent American population-based study reported an increase in VTE events from 1985 to 2009. While this may in part be due to more sensitive diagnostic methods, it may also imply that current prevention and treatment strategies are insufficient. Given the considerable economic burden of VTE imposed by both the management of acute events, and the costs associated with long-term complications, further research is warranted in order to improve risk stratification, prevention and management.
1.3 Risk factors for venous thromboembolism

Anything influencing the incidence of disease occurrence is called a risk factor. In epidemiology, a risk factor is generally a characteristic increasing the probability of developing disease. The impact of a risk factor depends on both its prevalence and the associated relative risk. VTE is a multifactorial disease, as several risk factors need to be present at the same time to induce thrombus formation. The thrombosis potential model is a useful explanatory model in this regard. In this concept, thrombosis risk depends on a dynamic, age-dependent interaction of both genetic and acquired risk factors. Each risk factor, such as FV Leiden or oral contraceptive use, adds to an individual’s thrombosis potential, culminating in thrombosis only when the joint effect of all risk factors outweighs natural anticoagulant properties (figure 2).

Figure 2. The thrombosis potential model. In this figure, the thrombosis potential model is illustrated in a hypothetical female carrier of factor V Leiden (FVL). In her teens, she starts using oral contraceptives (A). The combined effect of OCs and FVL does nevertheless not increase the thrombosis potential sufficiently to reach the thrombosis threshold. In scenario B, she is using OCs in her early thirties, and has a plaster cast after an accident. The combination of FVL, OCs and immobilisation reaches the thrombosis threshold, resulting in symptomatic VTE. In scenario C, she uses OCs in her late fourties. Now, FVL and OCs, combined with increased age, is sufficient to cause VTE. Adapted from Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999; 353: 1167-73.
1.3.1 Hereditary risk factors

Family studies have shown a strong heritability for VTE, with genetic factors accounting for approximately 60% of the variation in susceptibility to thrombosis. Inherited thrombophilias increase VTE risk mainly by two mechanisms, either by impairing natural anticoagulant pathways (loss-of-function) or by potentiating procoagulant pathways (gain-of-function). In general, the former is rare, but associated with a high thrombosis risk, whereas the latter is more common, but relatively less thrombogenic. Well known loss-of-function mechanisms include heterozygote antithrombin, protein C and protein S deficiencies, all of which increase VTE risk approximately 10-fold. These deficiencies are relatively rare, occurring in less than 1% of the general population, while being present in 1-3% of VTE patients. The factor V Leiden mutation, causing factor V resistance to the anticoagulant function of activated protein C, is prevalent in about 5% of Caucasians in its heterozygous form, while approximately 1 in 5000 are homozygote carriers. According to a recent meta-analysis, the odds ratio (OR) for VTE associated with factor V Leiden heterozygosity was 4.22 (95% CI 3.35-5.32), while homozygote carriers had an almost 12-fold increased risk (OR 11.45, 95% CI 6.79-19.29). The prothrombin G20210A gene mutation, resulting in increased prothrombin concentration, is relatively common, with a prevalence of 1-2% in the general population, although with a varying geographic distribution. Carriers of the prothrombin gene mutation have approximately 3-fold increased risk of VTE compared to non-carriers. As the factor V Leiden and the prothrombin G20210A gene mutations both are common, double heterozygocity is not exceptional, and associated with a twentyfold increase in VTE risk compared to individuals with neither mutation. The most frequent genetic risk factor for VTE identified so far is the non-O blood group, which doubles VTE risk. The Non-O blood group is associated with increased vWF and FVIII, presumably due to decreased proteolysis and clearance, but remains significantly associated with VTE even after adjustment for both factors. Conversely, both high plasma levels of FVIII and vWF are associated with VTE risk after adjustment for ABO blood group.

Although a significant proportion of VTE events may be attributed to genetic factors, the known thrombophilias identified so far only explain a small percentage of VTE heritability. The genome-wide association studies (GWAS) of the last decade have identified an extensive amount of new susceptibility loci to complex diseases. In most cases, however, identified risk alleles are common, but explain only a small percentage of the heritability of the disease. VTE is no exception; although several novel single nucleotide polymorphisms (SNP) associated with increased thrombosis risk have been identified through the GWAS
approach, they only have a modest effect of VTE risk and limited clinical utility. Whole-genome sequencing is an exciting, albeit time-consuming and expensive, approach to delineate novel genetic causes of VTE, and will hopefully lead us closer to unraveling the VTE mystery in the near future.

1.3.2 Non-hereditary risk factors

Advancing age is an established risk factor for VTE, and several studies have shown that the incidence of first-time VTE rises exponentially with age.\textsuperscript{16,43,44} In a previous study from the Tromsø population, subjects aged $\geq$ 70 years had an 11-fold higher risk of VTE compared to subjects < 50 years,\textsuperscript{44} and similar findings have been reported in the Longitudinal Investigation of Thromboembolism Etiology (LITE) study.\textsuperscript{43} The independent effect of age on VTE risk may be a result of increased levels of procoagulant proteins in the elderly\textsuperscript{45} or age-related changes in the vein walls or venous valves.\textsuperscript{7}

Obesity is a global epidemic and widely recognized as a major health threat, especially in Western countries. As the obesity prevalence escalates, VTE incidence will increase, as obesity is an important VTE risk factor. Historically, the year 2000 marked a turning point when the number of adults with excess weight surpassed the number of those underweight for the first time in human evolution.\textsuperscript{46} According to 2008 estimates from the World Health Organization (WHO), more than 1.4 billion people worldwide are overweight (body mass index (BMI) $\geq$ 25 mg/m$^2$) and 500 million people are obese (BMI $\geq$ 30 mg/m$^2$).\textsuperscript{47} A meta-analysis by Ageno and co-workers reported an OR of 2.33 for VTE in obese subjects, the association between BMI and VTE risk becoming stronger as the BMI increased.\textsuperscript{48} Previous publications from the Tromsø study in which anthropometric measures of overweight were studied, showed that increasing BMI, waist circumference and hip circumference were all positively associated with VTE, with weight circumference being the best predictor of risk.\textsuperscript{49} There are several possible mechanisms behind the association between obesity and VTE. Obesity is associated with elevated plasma levels of certain coagulation factors, such as tissue factor, fibrinogen, FVIII and vWF, and normal fibrin clearance is compromised by increased PAI-1.\textsuperscript{50} Furthermore, leptin, a hormone produced in adipose tissue and thus increased in the obese, is associated with increased thrombosis risk by both promoting platelet aggregation and inducing TF expression.\textsuperscript{51} Finally, the physical aspects of excess body weight may contribute to the increased risk, as obese subjects have chronically raised intra-abdominal pressure and impaired venous return.\textsuperscript{52}
The French physician Armand Trousseau described a relationship between malignancy and thrombosis as early as in 1865, and a year and a half later famously diagnosed himself with occult stomach cancer after suffering from phlebitis of the left arm. Approximately 20% of all first VTE events are cancer-associated, and cancer patients have a 4- to 7-fold increased risk of VTE compared to cancer-free subjects. Several pathophysiological changes may promote thrombosis in cancer, including platelet activation, decreased synthesis of anticoagulants and reduced clearance of coagulation factors. Furthermore, tumor cells may produce TF or shed TF-bearing microparticles. Thrombosis risk is also increased due to local tumor invasion and cancer treatment itself (surgery, chemotherapy, hormonal therapy, erythropoiesis-stimulating agents, central venous catheters and blood transfusions).

Hospitalization is another important risk factor for VTE. Hospitalized patients have a 100-fold increased risk of VTE compared to community residents, and in a nested case-control study, Heit and co-workers found factors associated with institutionalization to independently account for almost 60% of incident VTE cases. Both surgery and trauma increase VTE risk. A meta-analysis found surgery within the last 45-90 days to be associated with a 4- to 22-fold increased risk of VTE, and neurosurgery, hip replacement surgery and major vascular surgery are particularly high-risk procedures. The reported frequency of VTE among hospitalized patients after trauma varies, with estimates ranging from 1 to 58%. Major trauma patients who do not receive thromboprophylaxis have a DVT risk that exceeds 50%, and PE is the third most common cause of death in those who survive beyond the first day. Non-surgical hospital admissions are also associated with VTE risk, and 50-70% of symptomatic thromboembolic events and 70-80% of fatal PEs occur in these patients. From a general population perspective, hospitalization for an acute medical condition is associated with an 8-fold increase in VTE risk, and accounts for almost one fourth of all VTE events. Due to the large number of VTE events attributable to hospitalization, guidelines with prevention strategies are regularly updated and released. Despite these detailed practice guidelines, the underutilization of thromboprophylaxis in hospitalized patients still constitutes a major health problem, and implementation strategies to improve prescription routines are being investigated.

During the 1940 London Blitz of World War II, the pathologists reported a six-fold increase in the incidence of fatal PE in people who sat immobile in air raid shelters for long periods of time. A decade later, the renowned American surgeon John Homans described a case of DVT that occurred after a 14-hour long flight, leading him to conclude that VTE may occur after several situations involving prolonged sitting. Since these reports,
immobilization has been established as an important risk factor for VTE, and a meta-analysis including 4055 VTE cases found all-type travel to be associated with a nearly 3-fold increased VTE risk, with a dose-response relationship of 18% higher risk per each 2-hour increase in travel duration. In a large cohort of emergency department patients, VTE risk was substantially increased by the presence of limb, whole-body, or neurologic immobility.

Pregnancy is a known VTE risk factor, and VTE remains the leading cause of maternal death in the developed world. Pregnant women have a 4- to 5-fold increased risk of VTE compared to the non-pregnant population, and during the first six weeks postpartum, the risk is 20 to 80-fold higher. The predisposition to thrombosis in pregnancy is caused by a hormone-induced shift toward hypercoagulability, most likely developed to prevent fatal hemorrhage during delivery, and comprises both increased expression of clotting factors and reduced fibrinolytic activity. Furthermore, increased venous capacitance and decreased venous outflow, as well as mechanical obstruction by the uterus, may contribute to pregnancy-related thrombosis risk.

Exogenously administered combined oral contraceptives (COCs) and postmenopausal hormone replacement therapy (HRT) are also established risk factors for VTE. Depending on hormone type, hormone quantity and duration of use, COCs are associated with a 2- to 6-fold increase in VTE risk, while a meta-analysis reported a relative risk (RR) of 2.14 for VTE among current HRT users compared to non-users. Both COCs and HRT induce changes in the hemostatic system. Clotting factors are increased while coagulation inhibitors are reduced in women taking COCs, and there is an increased resistance to the anticoagulant action of activated protein C. In HRT users, procoagulant alterations of the hemostatic system are more pronounced in women taking conventional high dose HRT as compared with low-dose therapy, suggesting a threshold effect.

Despite the current knowledge of VTE risk factors, 25-50% of VTE events occur without apparent predisposing conditions, and are defined as unprovoked. It is imperative to continue ongoing research efforts to identify novel risk factors, adding new pieces to the VTE puzzle.

1.4 Arterial cardiovascular disease and the risk of venous thromboembolism
Arterial cardiovascular diseases (myocardial infarction (MI) and stroke) and venous thromboembolism are traditionally considered as different disease entities with different clinical manifestations, pathophysiology, risk factors and treatment. Arterial thrombosis generally arises on the rupture site of an atherosclerotic plaque, where shear stress is high,
resulting in platelet-rich, “white” thrombi, while venous thrombi occur in the slow-flowing venous system, on the surface of a largely intact endothelium, producing “red thrombi” rich in fibrin and erythrocytes. This clear-cut distinction was challenged in 2003, when Prandoni and co-workers reported that patients with unprovoked DVT had a higher prevalence of carotid atherosclerosis. In their study, patients with unprovoked DVT had an OR of 2.3 for carotid atherosclerosis compared with patients with provoked DVT, and an OR of 1.8 compared with hospitalized controls. These findings sparked an ongoing debate as to the extent of the interrelation between arterial and venous thrombosis. In a Swedish autopsy study, verified arterial thrombosis was positively associated with risk of VTE, and Sørensen et al reported an increased VTE risk in patients with a history of arterial cardiovascular events in a population-based registry study. Conversely, VTE as a risk factor for arterial cardiovascular disease (CVD) has also been examined. In studies of VTE patients, subjects with unprovoked events had higher risk of CVD than patients with provoked events. In a registry study of over 40,000 patients with VTE and 160,000 controls, a 2- to 3-fold increased risk of MI and ischemic stroke after a first VTE was shown; the risk being most pronounced in the first year following the initial event. A meta-analysis of published studies which included ischemic stroke and MI as endpoints concluded that VTE increased the risk of arterial thrombosis 1.9-fold. Given these findings, it is of pivotal importance to clarify the nature of the observed association between arterial cardiovascular disease and venous thromboembolism. Several potential models explaining the interrelation should be explored in this regard (Figure 3):

Figure 3. Possible associations between VTE and CVD

A. CVD may directly influence the risk of VTE and vice-versa.
B. CVD and VTE may share common atherosclerotic risk factors.
C. The observed association is caused by other risk factors or diseases that increase the risk of both outcomes.
In exploring potential common risk factors, most previous studies have not investigated the effect of atherosclerotic risk factors on VTE in the absence of development of arterial thrombosis. A competing risks approach to calculate cause-specific hazards for both CVD and VTE would be of interest in this regard. By calculating failure time to the first event, the opportunity that one event alters the risk of another is eliminated; as is the possibility of apparent common risk factors being confounders by acting as a proxy for cause. Furthermore, confirmation of an already established relationship between a known cardiovascular risk factor and risk of CVD would also ensure appropriate measurements and classification of the exposure variable.

1.5 Cardiovascular risk factors and the risk of venous thromboembolism

The observed relationship between arterial and venous thrombosis could be explained by common risk factors. In the last decade, several studies have investigated possible shared risk factors, yielding somewhat conflicting results. Of the traditional cardiovascular risk factors, age and obesity have shown the most consistent association with VTE. In an extensive follow-up study of 18,662 previously healthy male physicians, using a cause-specific hazards approach, the incidence of both CVD and VTE increased with age, but with varying strength of association; the increase across four decades of age being almost 13-fold for MI, whereas VTE incidence increased 5-fold.92 Similarly, BMI was associated with both outcomes, the association being strongest for VTE (RR per 1 kg/m² for MI 1.05, 95% CI 1.03-1.07, for VTE 1.11, 95% CI 1.07-1.14). A family history of MI, a strong and independent risk factor for MI, has also been robustly associated with VTE risk in prospective studies. In a large meta-analysis by Ageno et al, obesity, hypertension, diabetes and low HDL-cholesterol were all associated with increased VTE risk. However, the analysis was mostly based on case-control studies and could not adjust or stratify for important confounders. Prospective studies have failed to show a consistent association between diabetes, dyslipidemia, smoking and VTE. In the LITE study, smoking, hypertension and dyslipidemia did not increase VTE risk, while diabetes was positively associated with VTE. The Nurses’ Health Study, a prospective cohort of 112,822 female nurses, found that obesity, smoking and hypertension, but not diabetes and high cholesterol levels, were positively associated with pulmonary embolism. Similar results were reported from in the Copenhagen City Heart Study, where obesity, smoking and diastolic blood pressure were found to be risk factors for VTE, whereas cholesterol levels, triglyceride levels, and diabetes mellitus were not.
The observed inconsistencies regarding the impact of traditional cardiovascular risk factors on VTE risk may rely on differences in study design, study population, number of VTE events, outcome verification and unrecognized confounders. Nevertheless, there are similarities in effective treatments for CVD and VTE, supporting the concept of shared etiology. Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA), a rate-controlling enzyme in the endogenous cholesterol synthesis, and have established efficacy in both primary and secondary prevention of CVD.97 Recently, several studies have shed light on a possible beneficial effect in VTE as well.98,99 The large, industry-financed randomized controlled JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial found a significant reduction in VTE events in subjects treated with rosuvastatin compared to placebo,100 and a meta-analysis of observational studies reported an OR for VTE of 0.67 (95% CI 0.53-0.84) when comparing statin users to controls.101 Similarly, while acetyl salicylic acid (ASA) inhibits thrombus formation in the arterial circulation, a preventive effect has also been found for VTE,102 and both LMWH and warfarin have a role in CVD prevention.103-105

As 25-50% of incident VTEs occur without any detectable provoking factors, the search for novel risk factors is imperative. In general, most prospective studies have reported null findings on traditional cardiovascular risk factors as VTE predictors, with the exception of age and obesity,44,92,96,106,107 while several case-control studies have demonstrated positive associations.48,108-110 While cohort studies are advantageous in establishing a temporal relationship between exposures and outcomes, modifiable risk factors may change during long periods of follow-up, leading to an underestimation of the true association due to regression dilution. Time-dependent analyses with repeated measurements of exposure variables during follow-up may be used to approximate the true effect of a modifiable exposure over time. The robustness of the exposure variables may also be assessed by confirming a known exposure-outcome relation, such as the relationship between smoking and risk of MI, within the same study population. Apart from the Physicians’ Health Study, in which only male physicians participated,92 no study has investigated the impact of cardiovascular risk factors on VTE and MI using a cause-specific hazards method. A comparison of the risk of arterial and venous thrombosis by atherosclerotic risk factors within a general population would therefore be useful in order to formally evaluate differences in associations.
1.6 Postprandial lipemia and the risk of venous thromboembolism

Historically, triglycerides have been measured in the fasting state in order to decrease variability and achieve consistency of measurements. However, based on a typical Western dietary pattern, most people spend the majority of the day in a non-fasting, postprandial state, with continuous fluctuation in lipemia. While fasting triglycerides are associated with cardiovascular disease, controversy remains regarding the clinical usefulness of fasting triglycerides as an independent predictor of CVD, as multivariate adjustments, in particular for high density lipoprotein cholesterol (HDL), markedly diminish the observed effects. As early as 1979, nutritional biochemist Donald Zilversmit postulated that atherosclerosis largely is a postprandial disease caused by prolonged and increased exposure of dietary triglyceride-rich lipoproteins to the vascular wall. This has since been supported by several prospective studies that have indicated non-fasting triglycerides as independent predictors of future cardiovascular events. Lipoprotein lipase (LPL) is the major enzymatic regulator of postprandial lipemia by hydrolyzing triglycerides in chylomicrons (CM) and very low density lipoproteins (VLDL).

Postprandial lipemia may constitute a procoagulant state, influencing homeostasis through alterations of both blood coagulation and fibrinolysis. Postprandial lipemia increases both coagulation factor VII activation and endogenous thrombin generation, and elevated levels of PAI-1, the main inhibitor of the fibrinolytic system, have been observed in the postprandial phase. Furthermore, both intervention with omega-3 fatty acid supplementation and statin treatment have been reported to decrease postprandial coagulation activation. Fasting and postprandial triglyceride levels are strongly correlated, and hypertriglyceridemia, as measured in the fasting state, was associated with VTE risk in a case-control study by Doggen and co-workers. In their study, elevated triglyceride levels in postmenopausal women doubled VTE risk. Ageno et al found significantly higher fasting triglyceride levels in cases with unprovoked DVT in comparison to control subjects, and an Austrian case-control study reported similar results. Nevertheless, prospective studies both from the LITE and the Women’s Health Study have contested these findings, showing no association between VTE and triglyceride levels. To date, no study has investigated the role of postprandial lipemia in venous thromboembolic disease.

1.7 High-sensitivity C-reactive protein and the risk of venous thromboembolism

C-reactive protein (CRP), named after its ability to precipitate the C-polysaccharide of the Streptococcus pneumonia bacteria, is a sensitive systemic marker of inflammation and tissue
damage. Synthesized by hepatocytes, plasma CRP exhibits stable intra-individual levels in the absence of infection, comparable to those of total cholesterol concentration and systolic blood pressure. As novel immunoassays for CRP with greater sensitivity were implemented in the mid-1990s, studies emerged in which increased CRP values, even within the range previously considered normal, were associated with cardiovascular events. In a large meta-analysis of 22 prospective studies that adjusted for all Framingham risk variables, the relative risk of incident coronary heart disease was 1.6 for CRP-levels greater than 3.0 mg/L compared with levels below 1.0 mg/L. To what extent CRP is a mediator in vascular disease or merely a marker of atherogenesis has been a matter of debate. CRP binds to LDL and is also present in atherosclerotic plaques, suggesting a possible causal role in cardiovascular disease. However, CRP-related genotypes have not shown an independent association with CVD, and the large Emerging Risk Factors Collaboration analysis found considerable weakening of the association of CRP with coronary heart disease after adjustment for traditional cardiovascular risk factors and other inflammation markers.

Criteria for the measurement of high-sensitivity (hs-)CRP in order to improve cardiovascular risk stratification is nevertheless implemented in current guidelines from the American Heart Association (AHA).

In comparison to the vast amount of data on the role of CRP in arterial cardiovascular disease, comparatively little is known of its potential role in VTE. Clinically, DVT patients present all the cardinal signs of inflammation, namely heat, redness, swelling and pain, and CRP levels correlates with established VTE risk factors, such as advancing age, obesity, pregnancy and malignancy. CRP induced human peripheral blood monocytes to synthesize tissue factor in vitro, and infusion of human CRP in healthy volunteers increased both prothrombin fragment 1+2 and d-dimer levels, indicating activation of the coagulation cascade. Furthermore, experimental studies have shown both increased expression and activity of PAI-1 and decreased tissue plasminogen-activator-1 in human aortic endothelial cells incubated with CRP.

A limited number of studies have explored the role of low grade systemic inflammation, as measured by CRP, in VTE. A Norwegian population-based nested case-control study of 2000 participants, found an OR of 1.6 (95% CI 1.2-2.2) for VTE for subjects in the highest quintile of CRP as compared to the subjects in the lowest quintile. Similar findings were reported in the Atherosclerosis Risk in Communities (ARIC ) cohort, where subjects with CRP in the upper quintile had a multivariable hazard ratio (HR) of 1.74 (95% CI 1.09-2.79) for VTE compared to subjects in the lowest quintile of CRP. By contrast, CRP
was not predictive of future VTE in the prospective LITE study and Physicians’ Health study.\textsuperscript{129,144}

In order to identify possible shared risk factors for arterial and venous thrombotic disease, the role of hs-CRP in VTE merits investigation in a prospective study from a general population.

1.8 Carotid atherosclerosis and the risk of venous thromboembolism
The carotid arteries are superficially localized, relatively large vessels with limited movement, and thus easily available for ultrasound imaging. B-mode ultrasound of the carotid arteries provides measures of both intima-media thickness (IMT) and plaques, both widely used as surrogate measures of cardiovascular disease. The IMT is the distance from the lumen-intima interface to the media-adventitia interface of the far wall of the artery.\textsuperscript{145} IMT has been positively associated with subsequent cardiovascular events independent of all major risk factors.\textsuperscript{146} Similarly, CVD risk increases with increasing plaque burden.\textsuperscript{147-149} Although IMT and total plaque area (TPA) are strongly correlated, IMT measures may to a greater extent represent medial hypertensive hypertrophy related to hypertension, while formed plaques are clear manifestations of atherosclerosis.\textsuperscript{148} As a substantial proportion of strokes are attributable to hypertension,\textsuperscript{150} it is not surprising that some studies have found the risk of CVD per IMT difference to be higher for the end point of stroke than for MI.\textsuperscript{146} Conversely, carotid plaque area is strongly correlated with the extent of coronary artery disease,\textsuperscript{147} and in a previous publication from the Tromsø study, TPA was a stronger predictor of MI than was IMT.\textsuperscript{148}

Prandoni and co-workers were the first to report on carotid atherosclerosis as a possible risk factor for VTE.\textsuperscript{83} In their study, the OR for carotid plaques was significantly higher in patients with unprovoked DVT than in those with provoked DVT or in age- and gender-matched hospitalized controls without thrombosis after multivariate adjustment (OR 2.3, 95\% CI 1.4-3.7, and 1.8, 95\% CI 1.1-2.9, respectively). The mean IMT measures of the common carotid arteries were also larger in patients with unprovoked DVT than in both those with provoked thrombosis and control subjects.\textsuperscript{83} Because atherosclerosis is associated with platelet activation, increased thrombin generation and fibrin turnover,\textsuperscript{151} a possible prothrombotic state induced by atherosclerosis has been postulated as the mechanism behind the increased VTE risk. This hypothesis was supported by findings in another case-control study by Hong and co-workers, where more coronary artery calcifications were found in patients with unprovoked VTE compared to controls.\textsuperscript{152} Nevertheless, two prospective studies
did not find subclinical atherosclerosis measures to be predictive of VTE.\textsuperscript{153,154} The differences in study design, study populations and diverging findings of these few studies, taken together with the observed interrelation between manifest CVD and VTE, necessitates further investigation of carotid atherosclerosis as a risk factor for VTE in a prospective cohort study from a general population.
2. AIMS OF THE STUDY

The aims of the study were:

- To investigate the impact of traditional cardiovascular risk factors on the risk of myocardial infarction and venous thromboembolism in a population-based cohort study, using a cause-specific hazards approach.

- To examine whether patients with a history of unprovoked venous thromboembolism have increased postprandial lipemia compared with healthy controls from a general population.

- To assess whether low-grade inflammation, as measured by hs-CRP, is associated with increased risk of venous thromboembolism in a population-based cohort study.

- To investigate the impact of subclinical atherosclerosis, as measured by carotid intima-media thickness and total plaque area, on the risk of future myocardial infarction and venous thromboembolism, using a cause-specific hazards approach.
3. STUDY POPULATION AND METHODS

3.1 The Tromso Study
The Tromsø study is a single-centre, population-based study with repeated health surveys of the inhabitants of the municipality of Tromsø, Norway. Originally initiated in 1974 in order to investigate and help combat the high cardiovascular mortality in Northern Norway, the Tromsø study has gradually expanded to include a broad spectrum of diseases, and six surveys have been conducted so far. Three of the four papers included in this thesis (papers 1, 3 and 4) are based on data from the fourth survey of the Tromsø Study. The fourth survey was carried out in the period 1994–1995 and consisted of two screening visits with an interval of 4–12 weeks. All inhabitants aged > 24 years were invited to the first screening visit, and a total of 27,158 subjects participated (77% of the eligible population). All participants aged 55 to 74 years and 5–10% samples in the other 5-year birth cohorts (25-54 years and ≥ 75 years) were invited for a more extensive second visit. A total of 7,965 subjects attended both visits, with a response rate of 77% in women and 74% in men. The participants were followed from the date of enrolment in the Tromsø study until December 31, 2005, September 1, 2007, and December 31, 2010 for papers 1, 3 and 4 respectively. Follow-up time differed as the registration of outcome measurements was continuously updated.

3.2 Baseline measurements
Baseline data was collected by self-administered questionnaires, blood samples and physical examination by trained personnel. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846; Critikon Inc., Tampa, FL, USA). Participants rested for 2 minutes in a sitting position before three readings were taken on the upper right arm at 2 minute intervals. The average of the two last readings was used in the analysis. Non-fasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after one hour respite at room temperature and further analyzed at the Department of Clinical Biochemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by an enzymatic colorimetric method using a commercially available kit (CHOD-PAP for cholesterol, and GPO-PAP for triglycerides, Boehringer-Mannheim, Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Determination of glycosylated hemoglobin (HbA1c) in ethylenediaminetetraacetic acid (EDTA) whole blood was based on
an immunoturbidometric assay (UNI-MATES, F. Hoffmann-La Roche AG, Basel, Switzerland). Hs-CRP was analysed in thawed serum aliquots after 12 years of storage at -70°C, and 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. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Information on diabetes, current smoking and use of hormone therapy was collected from a self-administered questionnaire. In papers 3 and 4, the self-reported diabetes data were supplemented with data on confirmed diabetes from the Diabetes Registry of the Tromsø Study. Cancer diagnoses prior to baseline were obtained from the Cancer Registry of Norway.

3.2.1 Ultrasonography
High-resolution B-mode ultrasonography of the right carotid artery was performed by experienced examiners, with the use of an Acuson Xp10 128 ART ultrasound scanner equipped with a 7.5 MHz linear-array transducer. The far wall (FW) and near wall (NW) of the right common carotid artery (CCA), the bifurcation (bulb) and the internal carotid artery (ICA) (6 locations) were scanned for the presence of plaques. A plaque was defined as a localized thickening of the vessel wall of more than 50% compared with the adjacent IMT. Still images were recorded for each plaque and digitized using the Matrox Meteor II frame grabber card and Matrox Intellicam version 2.07. With the use of the Adobe Photoshop image-processing program (version 7.0.1), measurement of plaque area were made by outlining the perimeter of the plaque with the Lasso tool, and the plaque area was calculated as pixel values. For the resolution used in the present study, a plaque area of 167 pixels corresponded to 1 mm². Total plaque area was calculated as the sum of all plaque areas. Automated measurement of IMT was performed in 10-mm segments the FW and NW of the CCA, and the FW of the bulb. The mean IMT from the 3 preselected images was calculated for each location. If present in the predefined location of interest, plaques were included in the IMT measurements. The average of the mean IMT measured in all 3 locations (hereafter referred to as mean IMT) was used in the analyses.
3.3 Outcome measurements

3.3.1 Venous thromboembolism

All first lifetime VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. The university hospital is the only hospital in the region, and all relevant diagnostic radiology, outpatient consultations and hospitalizations are provided exclusively by this hospital. The relevant discharge codes were International Classification of Diseases (ICD) 9th Revision codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9 for the period 1994 to 1998, and ICD 10th Revision codes codes I26, I80, I81, I82, I67.6, O22.3, O22.5, O87.1, O87.3 for the period 1999 to 2010. The hospital discharge diagnosis registry included diagnoses from outpatient clinic visits and hospitalizations. The radiology procedure registry was searched in order to identify potential cases of objectively confirmed VTE that may have been missed due to coding errors in the hospital discharge diagnosis registry. Trained personnel systematically reviewed all relevant diagnostic procedures performed at the Department of Radiology during the study period to confirm all VTE events. An additional search through the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE, either as a cause of death or as a significant condition contributing to death, were identified. All medical records for potential VTE cases were reviewed by trained personnel, who were blinded with regard to baseline variables. Events identified by the hospital discharge diagnosis registry or the radiology procedure registry were verified and recorded as a validated outcome when all four of the following criteria were met: (1) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography (CT), perfusion-ventilation scan, 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 (warfarin, heparin or similar agents), thrombolytics or vascular surgery unless contraindications were specified in the medical record. VTE events deriving from the autopsy registry were recorded as outcomes when the autopsy record indicated VTE as a cause of death or as a significant condition contributing to death. The VTE events were further classified as provoked or unprovoked, based on the presence of provoking factors at the time of diagnosis. An event was classified as provoked if any of the following were present: surgery or trauma within the previous 8 weeks, acute medical conditions (acute MI, ischemic stroke or major infectious disease), active...
cancer, marked immobilization (bed rest for more than 3 days, wheelchair use or long distance air travel over 5 hours within the last 14 days prior to the event). If none of these factors were present, the event was classified as unprovoked.

3.3.2 **Myocardial infarction**

The Norwegian national 11-digit identification number allowed linkage to national and local diagnosis registries. All first-time events of myocardial infarction were identified by linkage to the diagnosis registries at the University Hospital of North Norway (outpatient diagnoses included), and the National Causes of Death Registry at Statistics Norway. Cases of possible incident non-fatal and fatal myocardial infarction were identified by a broad search for the International Classification of Diseases (ICD) 8th Revision codes 410-414, 427, 430-438 and 795-796 in the period 1969-1979, ICD 9th Revision codes 410-414, 427, 430-438, and 798-799 in the period 1980-1998 and thereafter for the ICD 10th Revision codes I20-I25, I47.1, I48, I60-I69, and R96, R98, R99. The Causes of Death Registry covers subjects registered as living in Norway at the time of their death, without regard to whether the death took place in Norway or abroad. All possible MI events were validated by an independent endpoint committee. The hospital medical records were retrieved for case validation. Information from the National Causes of Death Registry and from 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. We performed manual and/or electronic text searches in paper versions (used until 2001) and digital versions of hospital records for notes on myocardial infarction in all participants with one or more of the diagnoses mentioned above. Thus, a systematic text search for myocardial infarction was performed also in participants with one of the other diagnoses other than MI. We included all incident events classified as definite, probable or possible MI, based on a classification algorithm which included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports, when applicable (see appendix).

3.4 **The case-control study (paper 2)**

In the second paper included in this thesis (paper 2), patients with unprovoked VTE were recruited from the Tromsø study’s registry of VTE patients in the municipality of Tromsø. VTE subjects were eligible for inclusion if they were 20 to 80 years of age, had an unprovoked VTE event without recurrence 1 to 5 years before the investigation, and had stopped anticoagulant treatment at least 3 months before the investigation. Cases who
responded positively to our invitation letter were invited to a screening visit. For each VTE case, one apparently healthy person matched for age and gender was recruited from the sixth survey of the Tromsø study and underwent the same screening visit as the VTE patients. At the screening visit, a complete medical history, physical examination, and blood samples were taken, with special emphasis on exclusion criteria. A detailed interview on the occurrence of cardiovascular events (previous or current transient ischemic attacks, stroke, angina pectoris, and MI), recurrent venous thrombosis, diabetes mellitus, and other concurrent diseases was obtained with a self-administrated questionnaire that also included dietary habits, physical exercise, and alcohol consumption. In total, of the 37 VTE cases invited, 20 subjects met all eligibility criteria and were included in the study along with 20 healthy age- and gender-matched controls.

3.4.1 Fat tolerance test
A fat-tolerance test was conducted using a test meal prepared from standard porridge cream containing 70% of calories from fat (66% saturated fat, 32% monounsaturated fat, and 2% polyunsaturated fat). The test meals were served with two teaspoons of sugar, cinnamon, and two glasses (150 mL each) of sugar-free juice. The test meals were freshly prepared each morning. A weight-adjusted meal (1 g fat per kg body weight) was served at 8:00 a.m. and consumed during a 15-minute period. The participants were allowed to drink 350-mL calorie-free beverages and eat an apple during the following 8 hours. Blood samples for lipoprotein isolation, and serum- and plasma preparations were collected before the meal and every second hour during the next 8 hours.

3.4.2 Isolation of chylomicrons and VLDL
Chylomicrons were isolated by overlayering 8 ml EDTA plasma with 5 ml of NaCl solution in a cellulose nitrate tube (Beckman Instruments Inc, CA, USA) and centrifuged in a Beckman SW40 Ti swinging bucket rotor at 20,000 revolutions per minute (rpm) for 1 hour at 4°C. The CMs, with Svedberg flotation (Sf) rates > 400, were carefully removed by aspiration from the top of the tube. The baseline and 4 hour plasma samples were relayered with 5 ml 1.006 kg/L NaCl solution and subjected to ultracentrifugation at 40,000 rpm for 20 hours at 20°C. VLDL, with Sf 20-400 was carefully removed by aspiration from the top of the tubes. CMs and VLDL fractions were divided into three aliquots in cryovials and frozen at –70°C until further analysis.
3.4.3 Serum lipids and apolipoproteins

Serum lipids were analyzed on an ABX Pentra 400 (Horiba ABX Diagnostics, Montpellier, France) with reagents from Horiba ABX Diagnostics (Montpellier, France). Total cholesterol (CHOD-PAP) and triglycerides (GPO-PAP) were measured using enzymatic photometric methods provided by Horiba ABX Diagnostics, Montpellier, France. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured by selective inhibition colorimetric assays (LDL cholesterol direct and HDL cholesterol direct, respectively, ABX Diagnostics). Serum apolipoprotein (apo-)AI and apolipoprotein (apo-) B were analyzed by turbidimetry on Cobas Mira S with reagents from ABX Diagnostics.

3.4.4 NMR lipoprotein subclass analysis

Proton nuclear magnetic resonance (NMR) spectroscopy was used to determine mean particle sizes of the main lipoprotein classes (VLDL, LDL and HDL) along with concentrations of 10 lipoprotein subclasses (CM/large VLDL, medium VLDL, small VLDL, intermediate-density lipoprotein (IDL), large LDL, small LDL, also reported as medium small LDL and very small LDL, large HDL, medium HDL, and small HDL in fasting and 4-hours postprandial citrated plasma at LipoScience Inc., Raleigh, NC, USA. NMR-derived lipoprotein particle levels are based on the NMR signals that are characteristic of typical lipoprotein particles and are not actual lipid measurements. NMR data are directly proportional to the number of particles, independent of lipid or apolipoprotein per particle, which may show interindividual variation.

3.4.5 Lipoprotein lipase measurements

Eight hours after ingestion of the test meal, blood was drawn into vacutainers (Becton Dickinson, Meylan, Cedex, France) containing heparin as anticoagulant and the heparinized blood was immediately placed on ice. Unfractionated heparin was given as a bolus injection (100 international units (IU)/kg bodyweight) on the contra-lateral arm to mobilize LPL from the endothelial surface into the circulation. A second blood sample was obtained 15 minutes after heparin administration and immediately placed on ice. Heparinized plasma was recovered within 30 minutes by centrifugation (2000xg for 10 min) at 4°C, divided into aliquots of 1.0 ml in cryovials, flushed with nitrogen, and frozen at –70°C until further analysis. To analyse LPL activity, sonicated emulsion of $^3$H-oleic acid-labelled triolein in 10% Intralipid (Fresenius Kabi) was used as substrate. Samples were preincubated for 2 hours on ice with 0.5 vol goat antibodies to hepatic lipase (HL) to suppress HL activity. LPL...
activity was expressed as mU/ml corresponding to nmol of fatty acid released per minute at 25 °C. LPL mass was measured in post-heparin plasma with a commercial ELISA kit (MARKIT-M LPL ELISA, Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) according to manufacturer’s instructions.
4. MAIN RESULTS

4.1 Paper 1:
COMPETING RISK OF ATHEROSCLEROTIC RISK FACTORS FOR ARTERIAL AND VENOUS THROMBOSIS IN A GENERAL POPULATION: THE TROMSØ STUDY

The aim of this study was to examine and compare the impact of traditional atherosclerotic risk factors on the risk of arterial and venous thrombosis, using a cause-specific hazards model. Information on traditional atherosclerotic risk factors (age, gender, BMI, blood pressure, blood lipids, diabetes and smoking) was obtained by physical examination, blood samples and questionnaires from 26,185 participants of the fourth survey of the Tromsø Study in 1994-1995. Incident MI and VTE events were registered until December 31, 2005. Failure time (years) was calculated from baseline enrollment to the first event of MI or VTE, and all subjects had at most one of the two outcomes on the date of first occurrence. During a median of 10.8 years of follow-up, there were 1279 incident MI cases and 341 VTE events. In the cause-specific hazards model, advancing age was associated with both MI (HR per decade 2.34, 95% CI 2.25-2.43) and VTE (HR per decade 1.87, 95% CI 1.74-2.01). Furthermore, BMI was associated with a similar 1.2-fold increased risk of MI (HR per 3 kg/m² 1.16, 95% CI 1.11-1.21) and VTE (HR per 3 kg/m² 1.20, 95% CI 1.12-1.29). Male gender, self-reported diabetes, current daily smoking, higher levels of systolic blood pressure, diastolic blood pressure, triglycerides and total cholesterol, and lower levels of HDL-cholesterol, were associated with increased risk of MI, but not with VTE. Age was more strongly associated with MI than VTE, as subjects ≥ 70 years had a 23-fold higher risk (95% CI 19.81-27.46) of MI compared to subjects < 50 years, while the corresponding estimate for VTE was 10.54 (95% CI 7.81-14.22). Obese subjects (BMI ≥ 30 kg/m²) had a higher risk of VTE than of MI (HR for VTE 2.02, 95% CI 1.50-2.72, HR for MI 1.64, 95% CI 1.40-1.93). In conclusion, our findings imply that except for age and BMI, traditional atherosclerotic risk factors are not shared by arterial and venous thrombosis.
4.2 Paper 2:
POSTPRANDIAL LIPEMIA IS NOT INCREASED IN PATIENTS WITH PREVIOUS UNPROVOKED VENOUS THROMBOSIS.

This study was undertaken to investigate whether patients with a history of unprovoked venous thromboembolism had increased postprandial lipemia. 20 patients with a history of unprovoked VTE and 20 age- and gender-matched healthy controls were subjected to a standard fat tolerance test (1 g fat per kg body weight) with subsequent blood sampling every second hour for 8 hours. Lipids were measured by traditional methods and lipoprotein subclasses were determined by proton nuclear magnetic resonance (NMR) spectroscopy. As lipoprotein lipase is a key enzymatic regulator of postprandial lipemia, postheparin LPL activity, mass and LPL-specific activity were measured in both patients and controls. VTE patients had higher BMI (29.3 ± 4.2 vs 26.8 ± 3.5 kg/m², p = 0.08) and protein C concentrations (109 ± 24% vs. 94 ± 22%, p < 0.05) than controls, but no differences between groups were found for smoking status, blood pressure, serum lipids, apolipoproteins and other thrombophilic factors. Except for greater plasma concentration of total HDL particles in the postprandial state (p=0.05) among VTE patients, no significant differences were found in lipoprotein concentrations or particle size between VTE patients and controls neither before nor after ingestion of the fat rich meal. The postprandial lipemia, assessed by the incremental area under the triglyceride curve, was not different in VTE patients and healthy controls (5.0 ± 3.6 mmol/l/h vs. 5.3 ± 4.4 mmol/l/h, p = 0.81). No LPL measures differed between the two groups. In conclusion, our findings support the concept that postprandial lipemia is not involved in the pathogenesis of VTE.
The purpose of this study was to investigate the association between high-sensitivity C-reactive protein (hs-CRP) levels and risk of future VTE in a general population. Hs-CRP was measured in serum samples from 6426 participants, aged 25-84, and recruited from the second screening visit of the Tromsø Study in 1994-95. Incident first-lifetime VTE were registered until September 1st 2007. There were 209 validated first VTE events during 70,572 person-years of follow-up (median 12.5 years). The median time to event was 7.1 years, and a total of 82 VTE events (39.2%) were unprovoked. There was no increased risk of VTE per 1 SD increase in hs-CRP (HR 1.08, 95% CI 0.95-1.23) or across quartiles of hs-CRP (p for trend 0.6) in age- and gender-adjusted analyses. Further adjustment for BMI, smoking and diabetes did not alter the risk estimates. Subjects in the upper quartile of hs-CRP (>2.28 mg/l) had a multivariable-adjusted HR of 0.91 (95% CI 0.61-1.36) for total VTE compared to subjects in the lower quartile. Excluding subjects with a cancer diagnosis either prior to inclusion date or during follow-up (n=1,230) did not significantly alter our estimates. In subgroup analyses, hs-CRP levels showed no association with either unprovoked (multivariable HR per 1 SD 1.08, 95% CI 0.87-1.33) or provoked VTE (multivariable HR per 1 SD 1.01, 95% CI 0.85-1.21). In conclusion, our findings do not support a role for low-grade inflammation, as measured by hs-CRP, in VTE pathogenesis.
Atherosclerosis in the carotid arteries is an established risk factor for arterial cardiovascular disease. We wanted to investigate the effect of carotid atherosclerosis on the risk of myocardial infarction and venous thromboembolism in a general population, using a cause-specific hazards model. Mean intima-media thickness (IMT) and total plaque area (TPA) in the right carotid artery were measured with ultrasound in 6257 people aged 25 to 84 years who participated in the second screening visit of the fourth Tromsø Study in 1994 to 1995. Incident MI and VTE events were registered from date of enrollment to end of follow-up on December 31, 2010. During a median of 15.4 years of follow-up, there were 894 validated first MI cases and 256 VTE events. The overall crude incidence rates were 11.4 (94% CI 10.7-12.2) per 1000 person-years for MI and 3.3 (95% CI 2.9-3.7) per 100 person-years for VTE. Using a cause-specific hazards regression model with attained age as time scale, increasing TPA was associated with MI risk (p for trend <0.001) in both crude analysis and after adjustment for sex, total cholesterol, HDL-cholesterol, body mass index, smoking, diabetes mellitus, and hypertension (p for trend <0.001). In multivariable analysis, participants in the upper tertile of TPA had a 1.70-fold increase in MI risk compared with participants without plaques at baseline (95% CI 1.42–2.03). In contrast, TPA was not associated with VTE in either crude or multivariable-adjusted analysis. Comparable findings were observed for mean IMT, which was significantly associated with MI in both crude-adjusted and multivariable-adjusted analyses (P for trend <0.001), with an HR of 1.88 (95% CI, 1.45–2.45) for participants in the upper IMT quartile versus the lower IMT quartile. In contrast, IMT was not associated with VTE risk in either crude-adjusted or multivariable-adjusted analysis (p for trend=0.82 and 0.57, respectively). Mean common carotid far wall IMT was associated with MI after multivariable adjustment (HR per 1 SD increase in mean common carotid artery far wall IMT 1.10, 95% CI 1.03–1.17) but not with VTE (HR per 1 SD increase in mean common carotid artery far wall IMT 1.02, 95% CI 0.90–1.17). In conclusion, our study showed that carotid atherosclerosis, assessed by TPA and IMT, is a strong risk factor for MI, but not for VTE.
5. GENERAL DISCUSSION

5.1 Methodological considerations

5.1.1 Study design
Epidemiological studies seek to identify exposures that may affect the risk of developing certain health-related outcomes, and to quantitatively measure their effect. Nevertheless, finding an association between exposure variables and outcome variables is not the same as causality. Three of the four papers included in this thesis (papers 1, 3 and 4) are based on data from a population-based cohort study. In a cohort study design, participants are followed from the date of enrolment until they develop the outcome of interest or until end of follow-up, yielding both absolute and relative risk estimates in the form of incidence rates and relative risks. This study design has several advantages. The temporal sequence of exposure and outcome allows for some assessment of causality, as the possibility of the outcome affecting the exposure is excluded. Furthermore, cohort studies often include a large number of participants, which enhances the external validity and generalization of the study findings to the background population. By design, cohort studies enables assessment of multiple outcomes at the same time, and are ideally suited to examine rare exposures. On the other hand, a cohort study is an inefficient approach for investigating rare outcomes with long latency periods, as this is time-consuming, requires a large study population and may result in a high loss to follow-up. Cohort studies are also susceptible to bias and confounding, as exposures are not randomly assigned. Although several strategies exist in order to reduce confounding, factors that influence the outcome may nevertheless be poorly quantified, unavailable or unsuspected, causing residual confounding.

In paper 2, we used a case-control design, selecting 20 VTE patients and 20 age- and gender-matched controls before subjecting both groups to a standardized fatty meal. The case-control design is frequently referred to as a retrospective study, as information on prior exposures is collected after the outcome of interest has occurred. Proportions of exposure among cases and controls are compared, producing risk estimates in the form of odd ratios. Case-control studies are ideally suited to investigate rare diseases, and may be cost-effective and efficient as information about exposure and outcome can be collected simultaneously. However, case-control studies do not provide information on incidence, and a proper matching of controls may be difficult. Furthermore, control selection may introduce bias if the chosen controls are unrepresentative of the reference population. This is a particular problem
when cases and controls are recruited exclusively from hospitals. Hospital patients tend to have different characteristics than the general population, and if these characteristics are related to the exposure under investigation, the estimate of the association between exposure and disease will be biased. As recall ability is related to the significance of a past event, cases and controls may also remember and report exposure or outcome information differently, thus introducing bias. Furthermore, given its retrospective nature, a case-control study cannot be used to establish a cause-and-effect relationship. Temporal bias (reverse causality) occurs when the outcome is a determinant of the exposure, and not vice-versa. For instance, the observed association between CRP and VTE seen in some case-control studies may in fact reflect an altered inflammatory profile caused by the thrombotic event. As an individual’s lipid profile may be altered in the presence of an acute medical event, such as a VTE, we performed blood sampling at least a year after the VTE event in order to reduce the chance of temporal bias. We also selected cases and controls from the same community-based population and matched on age and gender, thus reducing the possibility of selection bias and increasing the generalizability of our findings.

In accordance with the Bradford-Hill criteria of causality, the randomized controlled trial (RCT) is considered the superior study design to establish causality. The experimental nature of the RCT permits manipulation of the exposure in order to alter the outcome. Furthermore, randomization allocates participants to intervention and control groups by chance, minimizing confounding. RCTs are nevertheless time-consuming, expensive and sometimes ethically unfeasible. Furthermore, eligibility criteria of RCTs are usually strict, selecting a homogenous group of participants for whom the intervention is presumed safe and likely to demonstrate an effect if one exists. Therefore, while the RCT has superior internal validity in order to establish causality, selection bias at inclusion may reduce the external validity, rendering the observational study the best alternative in many cases.

5.1.2 Generalizability
All types of epidemiological studies raise concerns about generalizability from the study sample to other populations. As RCTs are considered the gold standard of clinical research design, results from such trials are routinely applied for clinical care of large populations. However, if the trial population differs from the population in which the intervention is applied, the generalizability of the results may be limited. In a cohort study, proper inclusion and exclusion criteria, a high participation rate and minimal loss to follow-up are key factors in order to ensure the external validity of the study findings. Papers 1, 3 and 4 of this thesis
are based on data from the fourth survey of the Tromsø Study (Tromsø IV), in which all inhabitants of the Tromsø municipality aged ≥ 25 years were invited to participate. The overall attendance rate was high (77%), and the age and gender distribution of the study population does not differ greatly from other Western populations in terms of the incidence and prevalence of cardiovascular diseases and risk factor distribution. Furthermore, the VTE incidence reported in our studies is comparable to other Western populations,\textsuperscript{15,82,96} contributing to the external validity of our findings. In general, non-responders in population-based surveys tend to have lower socioeconomic status and higher mortality than attendees.\textsuperscript{160} The Tromsø IV survey experienced a lower attendance rate among those <40 years and those >80 years, affecting the generalizability toward these age groups. As participation required physical attendance at the study site, selection bias due to lower attendance rate in the severely ill or disabled is also likely to have occurred. In a case-control study, as used in paper 2 of the thesis, controls should be similar to cases in all respects other than having the outcome of interest. In our study, cases were matched on age and sex in order to assure case-control comparability, and as a result, differences in baseline characteristics between the two groups were negligible. Cases and controls were also selected from the same community-based population, thus increasing the generalizability of our study findings.

5.1.3 Confounding

In epidemiology, a confounder is (1) related to both the exposure and the outcome, (2) unevenly distributed between the groups being compared, and (3) not an intermediate step in the causal pathway between the exposure and the outcome.\textsuperscript{161,162} Confounding may lead to over- and underestimation of the true association between exposure and outcome, or even turn the direction of association. Much of the strength of the RCT study design lies in its ability to control for possible confounders, as the randomization by all accounts distribute these equally between the groups being compared. Nevertheless, a perfectly equal distribution of confounders is based on the assumption of an infinitely large study sample. While cohort studies by design are non-experimental and lack randomly assigned exposure classification, several strategies may be used to minimize confounding.

Restriction of study participants is an effective approach to reduce confounding.\textsuperscript{163} For example, gender imbalances cannot confound a study restricted to women only. Such analyses will nevertheless have reduced external validity. Another simple method is to stratify for confounders, e.g. separate the analyses by a stratification variable such as gender or age groups. In papers 1, 3 and 4 of this thesis, measures of potential confounders were included as
covariates in multivariable regression models. Multivariable regression analysis uses the data to estimate how confounders are related to the outcome and produces an adjusted estimate of the exposure effect. We performed multivariable proportional hazard analyses in order to consider the effect of atherosclerotic risk factors on VTE when other exposure variables were taken into account. Nevertheless, residual confounding may still be present. Possible sources of residual confounding are unknown confounders, imprecise definitions of potential confounders and lack of information about potential confounders. For instance, the use of lipid lowering drugs, and specifically statins, influences both exposure variables (hs-CRP, low density lipoprotein (LDL) cholesterol and carotid atherosclerosis) and possibly the outcome variable (VTE). At the screening visit for the Tromsø IV survey, only 1.5% of participants reported current use of lipid-lowering drugs. Given the dramatic increase in the prescription of statins seen across Europe over the last decades, statin use during the follow-up period may be an unrecognized confounder in our population. Furthermore, we did not have information on inherited thrombophilias available at baseline. Information on hereditary thrombophilias was nevertheless collected at the time of VTE diagnosis, and only 16% of those with an unprovoked event had a known thrombophilic factor registered. This suggests that the majority of unprovoked events were caused by other risk factors. To the best of our knowledge, inherited thrombophilias are not associated with traditional cardiovascular risk factors or C-reactive protein levels. A small case-control study measuring IMT and ankle/brachial blood pressure index in carriers of inherited thrombophilias and healthy controls, found no relation between subclinical atherosclerosis and thrombophilia. Thus, we do not believe that inherited thrombophilias are unrecognized confounders in our study.

Matching is a method for controlling confounding in case-control studies. It consists of selecting controls with characteristics homogeneous to those of the cases; in our study, cases and controls were matched on age and gender and derived from the same general population. Matching allows the execution of studies based on a smaller number of individuals than studies where controls are selected by randomization. The major limit of matching lies in its inability of producing estimates of the effect of the matching variables. Also, matching may introduce selection bias if the controls are unrepresentative of the population that produced the cases. For instance, using blood donors as a control group when assessing cardiovascular risk factors may yield biased results, as blood donation is associated with a reduction in cardiovascular events and a more favorable lipid profile.

An interaction effect occurs when the association between an outcome variable and a covariate vary over levels of a predictor variable. For example, although the absolute risk is
lower, carotid atherosclerosis confers a higher relative risk of CVD in younger than older subjects,\textsuperscript{170} i.e., age modifies the effect of the predictor (atherosclerosis) on the outcome (CVD). In our analysis, we consequently performed stratified analysis examining the risk of MI in subjects younger than and older than 60 years of age separately (paper 4).

5.1.4 Information bias and misclassification

The internal validity of a study implies validity of inference for the study population, and is a prerequisite for external validity.\textsuperscript{171} The internal validity is vulnerable to information bias due to misclassification. Misclassification may be differential (related to the occurrence of the disease) or non-differential (not related to the occurrence of disease). As exposure variables are measured prior to the development of disease in a prospective cohort study, exposure misclassification is generally non-differential. On the other hand, the case-control study design is prone to differential misclassification bias, as there may be intentional or unintentional differential recall of information about exposures or outcomes depending on an individual’s case-control status (recall bias). The presence of disease may affect both a subject’s perception of the causes and prompt his/her recall of possible exposures/risk factors. Thus, data about exposures is believed to be better remembered by cases and/or underreported by controls. Nevertheless, misclassification in case-control studies may also be non-differential, as remembering previous occurrences and exposures may be difficult for everyone, independent of case-control status.

In papers 1, 3 and 4, information on several baseline variables was gathered by self-administered questionnaires. In the cohort study design, the use of such questionnaires is a cost-efficient method of collecting vast amount of data from a large number of participants. Also, self-administered questionnaires may be preferable compared with interviewer-administered questionnaires in collecting data on sensitive topics, such as sexuality and alcohol use. Self-reported data is nevertheless a possible source of misclassification, as questions in questionnaires may be misunderstood or skipped entirely. For instance, the prevalence of self-reported diabetes found in our study (1.6%) is markedly lower than expected, and likely an underestimate of the true population prevalence. Other reports from the same time period estimated the prevalence of diabetes in Western populations to be approximately 5\%\textsuperscript{,172,173} Misclassification error is nevertheless probably similar between participants who will experience a VTE event and those who do not, and thus non-differential. For other self-reported exposure variables, such as smoking, self-reported questionnaires have been shown to have high validity.\textsuperscript{174,175} Information obtained through self-administered
questionnaires may also be validated by detecting effects of our exposure variables on other factors. We found an expected increased risk of MI by both self-reported smoking and diabetes consistent with that of other cohorts.\textsuperscript{176,177}

Blood samples for measurements of serum lipid levels were drawn in a non-fasting state for papers 1, 3 and 4. The use of non-fasting blood samples may represent another source of exposure misclassification, as current guidelines recommend fasting lipid measurements in the assessment of cardiovascular risk.\textsuperscript{178} As subjects with a Western dietary pattern spend most of the day in the postprandial phase, one might nevertheless argue that a non-fasting blood sample is a more accurate measurement of lipid status. Also, a recent report from the Emerging Risk Factors Collaboration found HRs for cardiovascular disease by lipid levels to be as strong in participants who did not fast as in those who fasted, thereby concluding that lipid assessment in CVD may be simplified by not requiring fasting blood samples.\textsuperscript{179}

Using stored frozen blood samples for analysis may introduce bias if the stability of the measured biomarker is affected by freezing, thawing or by storage itself. In our study (paper 3), hs-CRP was analyzed in thawed serum aliquots after 12 years of storage at -70 °C, without any freezing-thawing cycles before measurement. Prior studies examining CRP stability in frozen samples have found a high correlation between CRP values obtained before and after long-term storage.\textsuperscript{180,181}

Ultrasound assessments of IMT and TPA are also possible sources of information bias. To minimize errors, ultrasound technicians underwent a two-month training program prior to study start, and standard operational procedures were used. Previous reproducibility data on IMT and TPA measurements from the Tromsø IV study found both between-observer and intra-observer reproducibility to be acceptable.\textsuperscript{182,183} Measurement error increased with increasing IMT,\textsuperscript{182} indicating that estimates will be weaker in those with highest IMT levels.

5.1.5 Modifiable risk factors

Modifiable risk factors represent a possible limitation of cohort studies, especially when the time lapse between exposure and disease manifestation is long. In the three prospective studies included in this thesis, follow-up time varied between 10.8 to 15.4 years, while the exposure variables of interest were recorded at baseline only. As most cardiovascular risk factors are modifiable, some subjects’ individual risk profile may have changed during follow-up, leading to regression dilution bias and an underestimation of associations. Baseline measurements of exposure variables have been shown to underestimate the strength of the real
association with one-third during the first decade,\textsuperscript{184} enhancing the risk of false negative associations (type II errors). Nevertheless, in paper 1, our risk estimates for MI by cardiovascular risk factors were similar to and consistent with that of other cohorts,\textsuperscript{176,177} serving as an indication as to the robustness of the baseline variables. For CRP, the self-correlation coefficient of measurements repeated years apart is approximately 0.5, comparable to that of total cholesterol,\textsuperscript{126} and while we did not have repeated measurements available, time-dependent Cox’s regression analysis revealed no significant change in risk of VTE by hs-CRP over time. Carotid atherosclerosis assessment was performed at baseline only, and a participant’s atherosclerotic load may have changed over time. Previous studies have nonetheless found both single IMT and TPA measurements to be robustly associated with future cardiovascular endpoints,\textsuperscript{146,147,185} and in the large PROG-IMT collaborative project, no evidence of an association between individual IMT progression and the risk of subsequent cardiovascular events was found.\textsuperscript{185}

5.1.6 Missing values

Large cohort studies frequently have missing observations. Study participants may not respond adequately to questionnaires, they may be lost to follow-up, some laboratory samples may be lost or mishandled, or there may be difficulties during the physical examination leading to insufficient measurements. Missing data may be handled in several ways, none of which are completely satisfactory: (1) omitting variables which have many missing values, (2) omitting individuals who do not have complete data (available-case analysis/list-wise deletion), and (3) imputing missing values from the available data.\textsuperscript{186} Imputation refers to the replacement of missing variable by an estimated value of that variable, derived from the available observed data. A prerequisite for imputation is that the missing data is missing at random, i.e. given the observed data, the missingness mechanism does not depend on the unobserved data. Also, the validity of results from imputation depends on careful and appropriate modeling of the distribution of the missing data.

The main concern regarding missing values is whether their presence introduces bias. If the fact that an observation is missing is unrelated both to the unobserved value and the data available (i.e. missing completely at random), analyses of only cases with complete data gives valid inferences. Otherwise, available-case analysis may introduce bias if the number of excluded participants is high and differ significantly from the ones included, and statistical power may be reduced. In the prospective studies included in this thesis (papers 1, 3 and 4),
subjects with missing values were similar to the subjects included in analysis with regard to clinically relevant parameters, so we chose to perform available-case analyses.

5.1.7 Detection and validation of outcome

All incident VTE events in our study were registered retrospectively by using the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. As the university hospital is the exclusive provider of specialized health care services in the region, the probability of a complete VTE registry is enhanced. However, we cannot exclude that some VTE events may have been diagnosed and treated elsewhere, and therefore missed. VTE events were thoroughly validated in order to avoid false positive outcomes, and had to fulfill all the criteria listed in the Methods section.

Despite rigorous validation criteria, possible outcome misclassification cannot be excluded. Retrospective registration of events relies on accurate and complete information in the patient records in order to obtain valid outcomes. There were no standardized instructions available for the individual physicians who examined the patients and recorded the circumstances of the event in the medical records, and the assessment of provoking factors relied on the information provided for each patient. Nevertheless, the VTE events were validated by personnel blinded to baseline characteristics, so any misclassification would be non-differential. Information about previous VTE prior to baseline was unfortunately not available for the study participants who did not experience VTE during follow-up. Subjects with prevalent VTE who should have been excluded from the analysis might have been included and treated as healthy participants. However, as this concerns only a small fraction of the participants, the effects on the risk estimates would likely be negligible.

Incident MI events were also registered retrospectively. Qualified personnel adhered to a strict classification protocol in order to perform an accurate validation of each possible case. Nevertheless, the final decision in classifying an event as a case lied with the researcher examining the available information. Some MI events might have also have been missed as they were diagnosed and treated at other hospitals. For the retrieved cases, however, data on number of MIs observed at other hospitals and the geographical location of these hospitals were available. This showed that only a small part of the cases (4%) was observed at hospitals outside Tromsø.
5.2 Discussion of main results

5.2.1 Cardiovascular risk factors and the risk of venous thromboembolism

In accordance with previous reports, our study (paper 1) identified age and obesity as common risk factors for arterial and venous thrombosis. Traditional atherosclerotic risk factors, such as male gender, hypertension, dyslipidemia, self-reported diabetes, and current smoking showed an expected association with MI risk, but not with VTE. The Physicians’ Health Study is the only previous study to use a cause-specific hazards approach to assess the impact of CVD and VTE, albeit in a selected population of male physicians only. In agreement with our findings in a general population, they found advancing age and increasing BMI to increase both MI and VTE risk, while hypertension, elevated cholesterol, diabetes, smoking and physical activity (inverse) was significantly associated with MI, but not with VTE. This contrasts the findings of a meta-analysis, based on mainly case-control studies and selected prospective studies, where hypertension, diabetes, hypertriglyceridemia and low HDL cholesterol all were associated with VTE risk. Nevertheless, there was significant heterogeneity between the studies included in the meta-analysis, and the adjustment for important confounders, such as age and BMI, was not possible.

Some studies have reported an increased risk of VTE in men compared with women. In a recent review, Montagnana et al reported inconsistent findings regarding the influence of gender on a first VTE, but found a protective effect for female gender on recurrent events. In our present study, we did not find any association between gender and VTE, while the risk of MI was significantly increased in men. In contrast, male gender remained significantly associated with VTE after multivariate adjustments in a previous report from the Tromsø IV cohort. As male gender is an independent risk factor for MI, it is possible that the non-associative nature of gender and VTE found in our study can be explained by the competing risk of MI in the male population. Furthermore, age is a stronger risk factor for MI than for VTE, rendering male subjects relatively more susceptible for MI than for VTE at a given attained age. Previous studies have also found taller height to significantly increase VTE risk in men, suggesting that taller height may be an unrecognized confounder for the increased risk of VTE in men versus women reported in some studies.

In accordance with the LITE study, the Physicians’ Health Study and the Framingham Study, we did not find an association between current smoking and VTE. Our findings are also in agreement with a meta-analysis including 10 studies where smoking status was
reported, which found no relation between smoking and VTE (OR 1.15, 95% CI 0.92-1.44, p<0.00001). Nevertheless, we only assessed current smoking, with smoking as a dichotomous yes/no variable, and could thus not consider possible effects of smoking amount and duration. Several studies have reported an association between heavy smoking and VTE. In the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a population-based case-control study, both current and former smokers had higher VTE risk compared with those who had never smoked, but those who smoked heaviest or longest had the highest relative risk (RR 4.3, 95% CI 3.0-7.1), indicating a dose-dependent relationship. In a population-based study excluding subjects with cancer at baseline, Severinsen and co-workers similarly found that tobacco doses exceeding 20 g/day for women and 30 g/day for men were associated with a higher risk of VTE than lower smoking doses. In a recent publication from our research group, heavy smokers (> 20 pack-years) had an increased risk of provoked VTE (HR 1.75, 95% CI 1.14-2.69), but the association disappeared in cause-specific hazard analysis when failure times were censored at the occurrence of MI or cancer. Similar findings were reported in the Iowa Women’s Health Study, where the association between smoking and VTE was driven by cancer-related VTE. These results suggest that other predisposing factors or diseases attributable to smoking may be necessary for smoking to convey a VTE risk.

Hypertension is an established risk factor for CVD, and our risk estimates for MI by hypertension category (yes/no) were similar to those found in the Physicians’ Health Study and the large, multinational INTERHEART study. The pathophysiological rationale for a role of hypertension in venous thrombotic disease is less evident. Hypertension was associated with pulmonary embolism in the Nurses’ Health study, but our null findings on hypertension as a VTE risk factor corroborate that of other prospective studies, where an observed association between hypertension and VTE disappeared after adjustment for age.

Diabetes mellitus is associated with both increased coagulability and impaired fibrinolysis. However, previous studies have yielded conflicting results regarding the impact on diabetes on VTE risk. In the LITE study, diabetes (defined as fasting glucose > 7 mmol/L or non-fasting glucose > 11.1 mmol/L) was found to be associated with a 60% increased risk of provoked VTE, but not with unprovoked VTE. Other prospective studies have not found any relationship between diabetes and VTE. A meta-analysis reported a 1.4-fold increase in VTE risk for diabetes in unadjusted analysis, but a large population-based case-control study found no association between diabetes and VTE after adjustment for
hospitalization, major surgery or medical illnesses.\textsuperscript{196} As mentioned, self-reported data may be a source of information bias and misclassification, and the prevalence of diabetes in our study (1.6\%) was considerably lower than expected. Nevertheless, diabetes was associated with a 2.5-fold increase in MI risk, consistent with estimates from other population-based studies.\textsuperscript{176,187} Borch et al found an association between impaired glucose metabolism (defined as HbA1c $\geq$ 6.1\% and/or self-reported diabetes and/or confirmed diabetes from the diabetes registry of the Tromsø study), but the association disappeared after age-adjustment.\textsuperscript{197} Furthermore, in a recent publication from our research group, a significant linear trend for increased VTE risk across categories of HbA1c disappeared after adjustment for BMI, suggesting that high BMI in patients with diabetes may have confounded the observed association between diabetes and VTE found in some studies.\textsuperscript{197}

Modifiable risk factors represent a potential limitation of cohort studies such as ours, especially when follow-up is long, possibly biasing results toward the null due to non-differential misclassification. When comparing the impact of risk factors for atherosclerosis on risk of MI and VTE within the same population, it is nevertheless likely that the degree of random misclassification of exposure is similar for both outcomes. In a recent publication from the ARIC study, cardiovascular risk factors were updated serially in a cohort of 15,340 subjects who were followed for a mean of 15.5 years for the development of VTE.\textsuperscript{107} Using a time-dependent analysis, current smoking and obesity were the only cardiovascular risk factors associated with VTE risk.\textsuperscript{107} Based on the existing literature and our present findings, traditional cardiovascular risk factors, with the exception of age and obesity, do not appear to be independently associated with VTE.

5.2.2 Postprandial lipemia, dyslipidemia and the risk of venous thromboembolism
In the present study (paper 2), we found that neither the magnitude nor the duration of postprandial triglyceridemia was associated with unprovoked VTE. With the exception of postprandial total HDL particle concentration, neither concentrations nor particle size of lipoprotein subclasses differed between patients and healthy controls under fasting and postprandial conditions. While our study is the first to explore a possible relation between postprandial lipemia and VTE, dyslipidemia has been investigated as a possible VTE risk factor. Fasting triglycerides are major determinants of postprandial lipemia,\textsuperscript{198} and are associated with increased VII coagulant activity, impaired fibrinolysis and increased blood viscosity.\textsuperscript{199,200} Several case-control studies have found hypertriglyceridemia to be associated with VTE risk,\textsuperscript{108,201,202} but these studies were nevertheless limited by a selected study.
population\textsuperscript{108} and no covariate adjustment.\textsuperscript{201} Vaya and co-workers found triglycerides to be associated with DVT in a case-control study of 151 DVT patients and 194 healthy controls, but triglyceride levels lost their association after adjustment for BMI.\textsuperscript{202} In accordance with both the LITE-study, the Copenhagen City Heart Study and the cohort of Swedish men,\textsuperscript{43,96,106} a previous report from the Tromsø study found no association between total cholesterol, HDL-cholesterol, triglycerides and risk of VTE.\textsuperscript{44} By comparing the impact of these lipid markers on MI and VTE risk within the same population, we confirmed dyslipidemia as a risk factor for MI, but found no association with VTE (paper 1). The discriminatory impact of lipid levels on MI and VTE risk suggest that dyslipidemia does not play an important role in VTE etiology.

A report from the Tromsø study was the first to demonstrate an inverse relationship between HDL-cholesterol and coronary heart disease,\textsuperscript{203} and subsequent studies have confirmed HDL-cholesterol as a cardiovascular risk factor,\textsuperscript{204} with antiinflammatory, antiatherogenic and antithrombotic properties.\textsuperscript{205} Several studies have found HDL-cholesterol to be protective against VTE.\textsuperscript{108,201,206-208} Doggen and co-workers found that increased levels of HDL were associated with a 30% lower risk of VTE in a case-control study of post-menopausal women,\textsuperscript{108} and a prospective study of 770 VTE patients followed for the recurrence of VTE found subjects with high HDL-cholesterol and apolipoprotein A1 to be at lower risk.\textsuperscript{206} Furthermore, a polymorphism on the LPL gene associated with reduced LPL activity, low HDL cholesterol and increased triglycerides was associated with unprovoked VTE in a prospective study of male physicians.\textsuperscript{209} In contrast, other prospective studies have failed to demonstrate a relationship between HDL-cholesterol and VTE risk.\textsuperscript{43,44,125,210,211} Differences in methodology may explain these divergent findings. HDL levels are reduced during the acute phase response.\textsuperscript{512} Hence, a reduction in HDL cholesterol following an acute VTE event may explain the positive association between low HDL and VTE risk found in some case-control studies. In our study, we found similar baseline HDL cholesterol in cases and controls, and there was no difference in LPL activity, LPL mass or LPL-specific activity between the two groups (paper 2). Cases had higher total HDL-particle concentration in both the fasting and the postprandial state. This finding contrasts the results from Deguchi and co-workers, who reported lower fasting plasma concentrations of total HDL particles, large HDL particles, HDL-cholesterol and apo-A1 in male patients with unprovoked VTE (<55 years) than in healthy controls recruited among blood donors.\textsuperscript{207} Nevertheless, blood donation is associated with increased HDL-cholesterol,\textsuperscript{168,213} possibly biasing results. In a previous report from the Tromsø study, HDL-cholesterol was positively associated with increased risk of
unprovoked VTE in women,\textsuperscript{211} and a similar tendency was reported in the LITE-study.\textsuperscript{210} Exogenously administered estrogens increase both HDL-cholesterol\textsuperscript{214} and VTE risk.\textsuperscript{79} However, neither cases nor controls used estrogen supplementation in our study (paper 2), and adjustment for estrogen use did not attenuate the risk estimates in the Tromsø study report.\textsuperscript{211} Taken together, these findings challenge the pathophysiological relevance of the antithrombotic properties of HDL cholesterol in VTE etiology.

Given the inconsistencies of studies on the association between lipids and VTE, van Schouwenburg and co-workers investigated whether apolipoproteins are more strongly related to VTE than classical lipoproteins in the large population-based cohort of the Prevention of REnal and Vascular ENd stage Disease (PREVEND) Study. They found no association with VTE for either apolipoproteins (Apo-A1 and Apo-B) or lipoproteins, nor for their ratios.\textsuperscript{215} While an association between apolipoproteins and VTE have been demonstrated in a case-control setting\textsuperscript{207,216} and in women on hormone therapy,\textsuperscript{125} the PREVEND study findings are in agreement with results from the prospective LITE study, in which no association between Apo-A1 and VTE was demonstrated.\textsuperscript{210} We observed no difference in baseline apolipoproteins (Apo-A and Apo-B) between cases and controls in our study.

In arterial cardiovascular disease, statin treatment has documented efficacy in both primary and secondary prevention of adverse events.\textsuperscript{97} A recent systematic review of 19 randomized controlled trials of statins versus placebo found that statin use significantly reduced all-cause mortality, major vascular events and revascularizations in participants without evidence of CVD at inclusion,\textsuperscript{217} and risk of recurrent events were also reduced in statin users.\textsuperscript{218} Evidence of a beneficial effect of statins in VTE first emerged in the year 2000, when Grady and co-workers observed a reduction in VTE events in women receiving statins who were participating in a hormone replacement therapy trial.\textsuperscript{99} Similar findings have been reported in several observational studies,\textsuperscript{85,98,219} and secondary analyses from the JUPITER trial showed a substantial reduction in VTE risk in subjects treated with rosvuavstatin compared with placebo (HR with rosvuavstatin 0.57, 95% CI 0.37 – 0.86).\textsuperscript{100} Interestingly, the observed effect of rosvuavstatin treatment was independent of baseline lipid levels.\textsuperscript{100} As serum lipid levels fail to show a consistent association with VTE, it is therefore plausible that pleiotropic effects of statins, rather than lipid-lowering per se, may protect against venous thrombosis. This is further supported by the observation that of all lipid-lowering medication, only statins show a beneficial effect in VTE.\textsuperscript{98,99} Numerous antithrombotic properties of statins have been demonstrated both in vitro and in vivo, and may explain the observed reduction of VTE events. Statins inhibit thrombin generation by down-
regulation of tissue factor and by increased thrombomodulin expression, and also dampen platelet reactivity. The early reduction of cardiovascular events seen with statin use in the setting of acute coronary syndromes is in agreement with these findings.

The efficacy of statins in CVD prevention in the absence of hyperlipidemia has also been attributed to anti-inflammatory drug effects. Several studies have shown that statin therapy lowers CRP levels independent of LDL-cholesterol reduction, and the JUPITER trial demonstrated a significant reduction in cardiovascular events in normo-lipemic subjects with elevated hs-CRP levels. While it has been suggested that the effect of statins on venous thrombosis may also result from their anti-inflammatory abilities, our null findings regarding hs-CRP and VTE render this hypothesis unlikely. In a recent meta-analysis of both published and unpublished data from 29 randomized studies, Rahimi and colleagues found a non-significant reduction in VTE events in statin users versus non-users (HR with statins 0.89, 95% CI 0.78-1.01). While none of the studies included in the meta-analysis had VTE as a primary endpoint, these findings nevertheless suggest that the beneficial effect of statins on VTE risk is limited in primary prevention.

5.2.3 Low-grade inflammation and the risk of venous thromboembolism

In the present study, we did not find high-sensitivity C-reactive protein to be predictive of future development of VTE (paper 3). Our findings were consistent regardless of whether hs-CRP was investigated using a categorical or a continuous approach, and subgroup analyses revealed no association between either unprovoked or provoked VTE and hs-CRP. Given the vast amount of data on the role of subclinical inflammation in CVD, comparatively little is known about the relationship between low-grade inflammation and venous thrombosis. Our findings are nevertheless in agreement with other prospective studies regarding CRP as a VTE predictor. Using a nested case-control design in the Physicians’ Health Study, Ridker and co-authors found baseline CRP to be higher among men who later experienced MI or ischemic stroke, but not in those who developed VTE, compared to men without vascular events. In the PREVEND study, hs-CRP levels in the AHA high-risk category were not associated with incident VTE. While the generalizability of these results may be limited due to the inclusion of male physicians only or subjects with an elevated urinary albumin excretion, similar findings were also reported in the LITE study, in which the established population cohorts from the Cardiovascular Health Study (CHS) and the ARIC study were pooled. In this study, 19,237 participants were followed for a median of 7.8 years for the development of VTE. Baseline CRP levels were not different between participants who
experienced a VTE event during follow-up and those who did not, and in multivariable-adjusted analysis, CRP remained unassociated with VTE, even at high levels. In a later report from the ARIC cohort, in which CRP measurements were performed in a larger population sample, subjects with CRP in the upper quintile had 74% higher risk of VTE compared to subjects in the lowest quintile. However, the trend across quintiles of CRP was solely driven by the high risk of VTE in the upper quintile, in which CRP levels above 5.95 mg/L were included. Similarly, in a nested case-control study from the second Nord-Trøndelag Health Study (HUNT 2), the positive prediction of CRP for unprovoked VTE depended on the low risk in the lowest CRP quintile, and there was no gradient across quintiles when the lowest reference category was excluded. In the Leiden Thrombophilia Study, CRP levels were higher in VTE patients than in controls, but when the analysis was restricted to CRP levels below the 95th percentile of control values (9.75 mg/L), the difference disappeared. These findings contrast the association of CRP levels with the risk of CVD, where the increase in risk by CRP level is nearly linear, without an obvious risk threshold. Furthermore, CRP only predicted VTE within the first year between blood sampling and the VTE event in the HUNT 2 study, unlike the observed effect of CRP in CVD, where CRP levels have been found to predict MI and ischemic stroke years prior to the event.

The thorough validation of VTE events in our study population allowed for subgroup analysis of unprovoked and provoked VTE events separately. We did not find any association with hs-CRP levels for either group. Excluding participants with a cancer diagnosis either prior to inclusion or during follow-up did not alter the results. Luxembourg and co-workers reported elevated levels of hs-CRP in subjects with unprovoked VTE compared with subjects with provoked VTE and healthy controls. Nevertheless, hs-CRP measurements were only available in a subset of the examined population, thus significantly reducing sample size. In a case-control study by Vormittag et al, increased CRP levels were associated with unprovoked VTE independent of hereditary and laboratory risk factors, but lost its significance after adjustment for BMI.

Examining the role of inflammation in VTE, other inflammatory markers have also been investigated. Both IL-6, the main stimulus for CRP synthesis, IL-8 and serum amyloid A have been associated with VTE in case-control studies. Whether inflammation is a cause or a consequence of the thrombotic event can nevertheless not be inferred from these studies. In a prospective cohort study of 6068 Swedish men, several inflammatory plasma markers associated with CVD (fibrinogen, haptoglobin, ceruloplasmin, orosomucoid and alpha-1-antitrypsin) did not increase VTE risk. In another prospective study, using a nested case-
control design, Christiansen et al examined several inflammatory cytokines (tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, IL-6, IL-8, IL-10 and IL-12p70) as VTE risk factors, but none were associated with future thrombosis.\textsuperscript{234} Zacho and co-workers assessed hs-CRP as a VTE risk factor in both the Copenhagen General Population Study and the prospective Copenhagen City Heart study.\textsuperscript{235} Interestingly, hs-CRP remained associated with VTE risk after multivariate adjustments in the cross-sectional study, whereas the significant prediction of hs-CRP for VTE was lost after adjusting for confounders in the prospective cohort.\textsuperscript{235} Furthermore, CRP genotypes associated with increased serum levels of CRP were not associated with VTE in either study,\textsuperscript{235} corroborating findings from two previous case-control studies.\textsuperscript{236,237}

Cohort studies examining the role of CRP as a VTE risk factor have measured CRP a long time prior to disease manifestation, and may thus be subjected to misclassification and the possibility of null findings due to regression dilution.\textsuperscript{129,144,194} In our study, hs-CRP levels were measured in serum samples months to years prior to a VTE event, and may not accurately reflect inflammatory status over time. However, in a recent prospective study from the HUNT 2 population, in which several pro-inflammatory cytokines were investigated as VTE predictors, cytokine levels did not increase shortly before the thrombotic event.\textsuperscript{234} Furthermore, the adjusted regression-dilution ratio of log-CRP concentration was 0.58 (95\% CI 0.52-0.64) in the large Emerging Risk Factors Collaboration, indicating a year-to-year consistency similar to that of systolic blood pressure and total cholesterol concentration in the same individuals.\textsuperscript{127} Vormittag et al found little intra-individual variation in hs-CRP values in a sample of 22 VTE patients with two hs-CRP measurements three months apart.\textsuperscript{228} Repeated-measurements analysis of hs-CRP as a risk factor for VTE has not been performed in a prospective design. Nevertheless, in time-dependent Cox regression analysis, we found no significant change in the risk of VTE by hs-CRP over time (p=0.3).

In sum, the majority of current available evidence points against a role of low-grade inflammation in VTE etiology. Nevertheless, overt clinical infection is a risk factor for VTE,\textsuperscript{238,239} and CRP levels are elevated in acute VTE events.\textsuperscript{240,241} As previously mentioned, the deep recesses of the venous valve cusps are predilection sites for venous thrombus initiation.\textsuperscript{7} Conditions that lower oxygen tension in the valve cusps, such as septicemia and prolonged immobilization, induces the upregulation of multiple stress-response genes in the venous endothelium.\textsuperscript{7,242} The endothelium is converted to a proinflammatory and procoagulant phenotype, characterized by the production of PAI-1 and the exposure of vWF and p-selectin from Weibel-Palade bodies, recruiting leucocytes, TF-bearing microparticles
and platelets. In turn, the recruitment and activation of these actors may result in increased secretion of inflammatory cytokines and TF exposure, initiating thrombus formation.\textsuperscript{7,242} Thus, while chronic low-grade inflammation does not appear to be associated with risk of future VTE, a localized prothrombotic and inflammatory response at the level of the venous valve sinus appears to be important in VTE pathogenesis.

5.2.4 Carotid atherosclerosis and the risk of venous thromboembolism
We found no association between carotid atherosclerosis, as measured by TPA and IMT, in neither crude nor multivariable-adjusted analyses in our study (paper 4). For the MI endpoint, our risk estimates increased over levels of TPA and IMT, and were of similar magnitude to those of other cohorts.\textsuperscript{170,185,243} While our study is the first to examine the effect of carotid atherosclerosis on VTE risk while accounting for the competing risk of MI, two other prospective, population-based studies have examined subclinical atherosclerosis as a VTE risk factor.\textsuperscript{153,154} In the ARIC study, 13,081 adults were followed for mean of 12.5 years. Measurements of IMT and the presence of plaques were assessed by carotid ultrasonography at baseline. An apparent dose-response relation was found between IMT thickness and VTE risk, but this association disappeared after adjustment for age, gender and ethnicity.\textsuperscript{154} Similar findings were reported in the Cardiovascular Health Study (CHS), where no subclinical atherosclerosis measurements (IMT, presence of plaques, ankle-brachial blood pressure index and electrocardiogram abnormalities) were associated with VTE in a cohort of older participants.\textsuperscript{153}

A few case-control studies have assessed the presence of atherosclerosis in VTE subjects compared with healthy controls. Prandoni and co-workers were the first to suggest an association between atherosclerosis and VTE.\textsuperscript{83} In their frequently cited paper, a higher prevalence of carotid plaques was found in patients with previous unprovoked DVT compared with patients with previous provoked DVT and hospitalized controls.\textsuperscript{83} Similarly, the presence of coronary artery calcium, a marker of systemic atherosclerosis, was significantly associated with VTE in a case-control study by Hong et al.\textsuperscript{152} In the former study, the examined participants were older than our population, and the definition criteria for carotid plaques were slightly different. Also, the healthy control group consisted of randomly selected patients admitted for conditions unrelated to VTE or atherosclerosis. Hong and co-workers used control subjects in which VTE was suspected, but later excluded. The risk factor distribution in the control groups of these studies may therefore be different from that of the background population, and these subjects likely differ in a number of unknown ways from a
random sample of subjects. Furthermore, the case-control design of these studies does not allow for certain establishment of temporality between cause and effect. These limitations also apply to a small case-control study from Bilora and co-workers, in which subclinical atherosclerosis was assessed by ultrasonographic IMT and plaque measurements in multiple arterial segments in 16 subjects with a history of provoked DVT and in 19 controls. In their study, comparable plaque distribution, plaque numbers and mean IMT values were observed in the two groups.

In our study, only the right carotid artery was scanned for the presence of plaques and the measurement of IMT, whereas measurements on both sides might have been more representative of the individual's plaque and IMT status. A previous study found significantly thicker IMT in the left CCA segment compared to that of the right, but no differences were found in IMT in the bulb or internal carotid artery segments or in plaque prevalence between the left and right carotid. As with all modifiable exposures, a participant’s atherosclerotic load may have changed over time, and we did not have sufficient data to properly adjust for statin use during follow-up. Nevertheless, our robust risk estimates for MI by carotid atherosclerosis measures suggests that our null findings for TPA and IMT as VTE factors are not explained by improper classification of the exposure variables. In conclusion, our findings corroborate previous reports for population-based prospective studies, suggesting that atherosclerosis does not contribute to VTE etiology.
6. CONCLUSIONS

- In our study, we found advancing age and obesity to be shared risk factors for MI and VTE. Other atherosclerotic risk factors, such as male gender, hypertension, dyslipidemia, self-reported diabetes and current daily smoking were associated with increased risk of MI, but not with VTE. Our findings imply that the link between arterial and venous thrombosis is not explained by the sharing of traditional atherosclerotic risk factors.

- We found no association between postprandial triglyceridemia measures and unprovoked venous thromboembolism. With the exception of postprandial total HDL particle concentration, neither concentrations nor particle size of lipoprotein subclasses differed between patients and healthy controls under fasting and postprandial conditions.

- Serum levels of hs-CRP were not associated with increased risk of venous thromboembolism in either crude or multivariable-adjusted analysis. Our findings were consistent regardless of whether hs-CRP was examined as a continuous or a categorical variable. Furthermore, Hs-CRP showed no association with either unprovoked or provoked VTE in subgroup analysis, suggesting that low-grade inflammation does not play a causal role in VTE pathogenesis.

- We found that subclinical atherosclerosis, measured by carotid IMT and TPA, conferred an increased risk of MI, with risk estimates increasing over levels of both IMT and TPA in multivariable-adjusted analysis. In comparison, no atherosclerosis measures were associated with VTE, suggesting that subclinical atherosclerosis is not a shared risk factor for MI and VTE.
7. FINAL REMARKS AND FUTURE PERSPECTIVES

Based on the existing literature and the findings of our present study, cardiovascular risk factors do not appear to be individually associated with VTE risk. Nevertheless, multiple studies have demonstrated an increased risk of future arterial cardiovascular events in subjects with a history of VTE.\textsuperscript{86-90,246} Other factors than those traditionally associated with atherosclerosis may be present and could possibly explain the association. While the traditional inherited thrombophilias are only weakly associated with increased risk of MI,\textsuperscript{247} high levels of several coagulation factors, including factors VIII, IX and XI, vWF and PAI-1, have been associated with arterial thrombosis.\textsuperscript{248,249} Furthermore, a family history of MI is associated with both future MI and VTE,\textsuperscript{44,93,94} suggesting a common genetic component for both diseases. The present era of whole-genome sequencing is exciting in this regard, and will hopefully provide some insight into the complexity of the interrelation between arterial and venous thrombosis in the years to come.

It is also possible that the association between VTE and CVD is restricted to the events themselves or their treatment. In a recent study by Lind et al, PE was a stronger predictor for MI than DVT.\textsuperscript{246} It can thus be hypothesized that a PE induces disturbances in the cardiopulmonary circulation that result in coronary artery thrombosis, either by a paradoxical emboli through a patent foramen ovale or through local prothrombotic changes. Furthermore, VTE treatment with vitamin K antagonists may lead to increased arterial calcification,\textsuperscript{250} thereby increasing MI risk. It is nevertheless unlikely that these associations fully explain the increased risk of MI observed in VTE patients. As cancer and cancer treatment are established risk factors for both VTE and MI,\textsuperscript{58,251-253} it would be interesting to explore cancer as a risk factor for both MI and VTE within the same population.

A majority of null findings for cardiovascular risk factors and VTE has been reported from several observational studies. As many of these risk factors are modifiable over time, a supplement to our cause-specific hazards approach would be a repeated-measurements analysis, in which the traditional atherosclerotic risk factors are assessed at several time points. To the best of our knowledge, the study by Wattanakit et al is the only study to date to perform a time-dependent analysis of atherosclerotic risk factors in VTE.\textsuperscript{107} The Tromsø study is ideal in this regard, as participants are re-examined at several time points. The ongoing registration and validation of VTE events in the Tromsø study population will allow for the execution of time-dependent analyses with sufficient follow-up time in the near future.
8. REFERENCES


Paper 1
Paper 2
Paper 4
Appendix
### Classification algorithm for myocardial infarction (MI). The Tromsø Study.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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| Definite MI     | Definite myocardial infarction was defined by one of the following sets of conditions:  
(a) Typical, atypical, or inadequately described symptoms + a definite new infarction in ECG recordings  
(b) Typical symptoms + significantly higher myocardial enzyme and/or troponin levels  
(c) Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels + a probable new infarction in ECG recordings  
(d) post-mortem evidence of recent myocardial infarction or thrombosis.                                                                                                                                                                                                                                                                                               |
| Probable MI     | Probable myocardial infarction was defined by one of the following sets of conditions:  
(a) Typical, atypical, or inadequately described symptoms + a probable new infarction in ECG recordings + moderately increased myocardial enzyme and/or troponin levels  
(b) Typical symptoms + moderately higher myocardial enzyme and/or troponin levels  
(c) Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels  
(d) Atypical or inadequately described symptoms + moderately higher myocardial enzyme and/or troponin levels + probable new infarction in ECG  
(e) Sudden death with no evidence of non-coronary cause of death.                                                                                                                                                                                                                                                                                                 |
| Possible MI     | An event that can be dated and where secondary data of a typical history in combination with ECG findings and/or echogradiography and/or autopsy are consistent with MI, but where no primary data source is available.                                                                                                                                                                                                                                                                                              |
| Unstable angina | Angina at rest or minimal exertion and ST-depression or negative T-wave in ECG.                                                                                                                                                                                                                                                                                                                                                         |
| Unclassifiable  | Increase in troponins or enzymes in relation to cardiac revascularization proc (PCI or CABG), or otherwise unclassifiable.                                                                                                                                                                                                                                                                                                                                                   |
| Silent MI       | In the absence of clinical symptoms that can be dated:  
(a) New diagnostic Q-wave in incidental ECG or  
(b) evidence of MI on echocardiograph and/or multi-gated acquisition scan or  
(c) evidence of MI at autopsy                                                                                                                                                                                                                                                                                                                                         |
| No MI           | When the conclusion after the validation procedure is that the event does not fulfill the criteria for an acute coronary event.                                                                                                                                                                                                                                                                                                                                                   |

ECG; electrocardiography, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft surgery
You are invited to the large health survey in the municipality of Tromsø 1994 - 95

We will reach everyone
We will start in the outskirts of the municipality. Here, the examination will take place in schools and other premises – see the information in the invitation accompanying this letter. From late October 1994 until summer 1995, the examination will take place in Mellomveien 50 (the Elisabeth centre; the old maternity hospital). We prefer that you attend at the location specified in the invitation letter.

Why did you receive this offer?
Because we offer this examination to everyone born 1969 or earlier.

What is the purpose?
The survey is first and foremost aimed at cardiovascular diseases, but is also important to gather new knowledge about other serious chronic diseases (amongst them cancer). This time we will also study musculo-skeletal pain conditions, for instance fibromyalgia. Therefore, some people will be invited to a separate examination in the fall of 1995. Large cardiovascular surveys were carried out in Tromsø in 1974, 1979-80, and 1986-87. The attendance rate was high, and several cases of cardiovascular disease were detected – who are now being treated. The surveys have also contributed with important knowledge to combat these diseases. The knowledge we gained through the previous surveys, made the University of Tromsø to one of the renowned research centres in the world with regard to cardiovascular diseases. Again, we aim to detect hitherto undiscovered cardiovascular disease. We also hope to reach those at particular high risk, so that they may get the possibility of prevention and other measures to stop the development of disease. Cardiovascular diseases are still one of our largest health problems.

Not only for your own sake ...
The examination not only is important for you personally. It is also important that the results may be used in medical research, for instance by using them together with information about disease that occur in the future. Thereby we will learn more about how cardiovascular diseases, cancer, and other population diseases develop, and how they may be prevented. By attending the survey, you are helping to fight these diseases.

The examination includes
- Measurement of height and weight
- Measurement of blood pressure
- Blood sample. In this sample, we will measure the content of lipids (e.g. cholesterol), calcium and a liver enzyme. The result of these measurements will be forwarded to your doctor if you consent. The result of other analyses will be used for medical research only. The blood sample will be frozen to make it possible to perform other blood analyses in order to study disease development. Before such analyses are performed, the study will be presented to the Regional Ethical Committee of North Norway.

ECG is a test that registers the heart activity. We will use a simplified version, and the results will be used for research purposes only.
**Questionnaire**

This you will find on the reverse side of the invitation letter. Please fill in the questionnaire beforehand and bring it to the examination site. If some questions are difficult to answer, you may get some help when you attend.

**Follow-up examination**

Some of those who are examined may later be referred to their own doctor for a more thorough control. If you are in need of treatment, you will be offered such treatment.

**What does it cost?**

A small fee is necessary for this examination. It is very modest compared to the actual cost. You will find the amount in the letter you have received now. The special examination is free of charge. If you will need an examination by your own doctor or at the Regional hospital, you will have to pay the ordinary fee.

**Clothing**

Because of the blood pressure measuring, we ask you to wear clothes that are sleeveless or with short sleeves that are not tight. It is not necessary to take the clothes off.

**Places that will be visited by the health survey**

- Kaldfjord
- Tromvik
- Lakselv bukt
- Sjursnes
- Breivik bodet
- Fagernes
- Skottet
- Erdfjordbott
- Straums bukt
- Brenesholmen
- Vikran
- Trondjord
- Sjøtun
- Tromsø sentrum

**Welcome!**

Sincerely

- The municipality health service
- The Faculty of medicine, University of Tromsø

(Heartily welcome, dear Tromsø inhabitant)
The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

We would like you to fill in the form overleaf and take it with you to the examination.

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that you will be able to come. Attend even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure measured recently.

Yours sincerely,

Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service
YOUR OWN HEALTH

What is your current state of health? Tick one box only.

- Poor ........................................ 12
- Not so good .................................. 2
- Good ......................................... 3
- Very good .................................. 4

Do you have, or have you had:

- A heart attack ................................ 13 years
- Angina pectoris (heart cramp) .......... 16 years
- A cerebral stroke / brain haemorrhage 19 years
- Asthma ......................................... 23 years
- Diabetes ....................................... 25 years

Do you use blood pressure lowering drugs?

- Currently ...................................... 1
- Previously, but not now ..................... 2
- Never used .................................... 3

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months?

Have you in the last two weeks felt:

- Nervous or worried? ......................... 30
- Anxious? ....................................... 31
- Confident and calm? ......................... 32
- Irritable? ...................................... 33
- Happy and optimistic? ....................... 34
- Down/depressed? ............................ 35
- Lonely? ........................................ 36

Put 0 if you do not spend time in smoke-filled rooms.

Did any of the adults at home smoke while you were growing up? ........................................ 37

Do you currently, or did you previously, live together with daily smokers after your 20th birthday? .................. 38

If "YES", for how many years in all? .......... 39

How many hours a day do you normally spend in smoke-filled rooms? ....... 41

Put 0 if you do not spend time in smoke-filled rooms.

Do you yourself smoke:

- Cigarettes daily? .......................... 43
- Cigars/ cigarillos daily? ................. 44
- A pipe daily? ................................. 45

If you previously smoked daily, how long is it since you quit? .................. 46

If you currently smoke, or have smoked previously:

- How many cigarettes do you or did you usually smoke per day? .......... 48
- How old were you when you began daily smoking? .................. 52
- How many years in all have you smoked daily? .................. 54

EXERCISE

How has your physical activity in leisure time been during this last year? Think of your weekly average for the year. Time spent going to work counts as leisure time.

- Light activity (not sweating/out of breath) ................................ 56
- Hard activity (sweating/out of breath) ..................................... 57

Put 0 if you do not drink coffee daily.

How many cups of coffee do you drink daily?

- Coarsely ground coffee for brewing ................................... 58
- Other coffee .................................... 60

ALCOHOL

Are you a teetotaller? ................. 62

How many times a month do you normally drink alcohol? Do not count low-alcohol beer.

Put 0 if less than once a month. ......... 63

How many glasses of beer, wine or spirits do you normally drink in a fortnight?

- Beer ........................................ 58
- Wine ........................................ 59
- Spirits ....................................... 60

FAT

What type of margarine or butter do you usually use on bread? Tick one box only.

- Don't use butter/margarine .............. 71
- Butter ........................................ 72
- Hard margarine .............................. 73
- Soft margarine .............................. 74
- Butter/margarine mixtures .............. 75
- Light margarine ............................ 76

EDUCATION/WORK

What is the highest level of education you have completed?

- 7-10 years primary/secondary school, modern secondary school .......... 72
- Technical school, middle school, vocational school, 1-2 years senior high school .......... 73
- High school diploma (3-4 years) ........................................ 74
- College/university, less than 4 years ....................................... 75
- College/university, 4 or more years ...................................... 76

What is your current work situation?

- Paid work .................................... 73
- Full-time housework ......................... 74
- Education, military service .................. 75
- Unemployed, on leave without payment ....... 76

How many hours of paid work do you have per week? .......... 77

Do you receive any of the following benefits?

- Sickness benefit (sick leave) ................. 79
- Rehabilitation benefit ......................... 80
- Disability pension .......................... 81
- Old-age pension ................................ 82
- Social welfare benefit ......................... 83
- Unemployment benefit ......................... 84

ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp) ? ............. 85
The Tromsø Health Survey

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire ........................................... 17

Date for filling in this form:................................................................. Day Month Year

HOME

Who do you live with?
Tick once for each item and give the number . Yes No Number

<table>
<thead>
<tr>
<th>Family member</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouse/partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other people over 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People under 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How many of the children attend day care/kindergarten? .... 18

What type of house do you live in?

<table>
<thead>
<tr>
<th>Type of house</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villa/detached house</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat /apartment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terraced /semi-detached house</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How big is your house? .................................................................... 46 m²

Approximately what year was your house built? ........... 49

Has your house been insulated after 1970?............ 53

Do you live on the lower ground floor/basement? ...... 54

If "Yes", is the floor laid on concrete? ............... 55

What is the main source of heat in your home?

<table>
<thead>
<tr>
<th>Source of heat</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electric heating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood-burning stove</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central heating system using:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraffin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electricity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you have fitted carpets in the living room? ............ 57

Is there a cat in your home? ....................................... 58

Is there a dog in your home? ..................................... 59

WORK

If you have paid or unpaid work, how would you describe your work?

<table>
<thead>
<tr>
<th>Type of work</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly sedentary work?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. office work, mounting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work that requires a lot of walking?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. shop assistant, light industrial work, teaching)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work that requires a lot of walking and lifting?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. postman, nursing, construction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy manual work?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. forestry, heavy farm-work, heavy construction)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Can you decide yourself how your work should be organised?

<table>
<thead>
<tr>
<th>Decision level</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, not at all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a small extent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, to a large extent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, I decide myself</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are you on call, do you work shifts or nights? ....... 60

Do you do any of the following jobs (full- or part-time)?

<table>
<thead>
<tr>
<th>Job</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisherman</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1 year?

<table>
<thead>
<tr>
<th>Municipality</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you did not live in Norway, give country of residence instead of municipality.

How was your family's financial situation during your childhood?

<table>
<thead>
<tr>
<th>Financial situation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very difficult</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How many of the first three years of your life
- did you live in a town/city? ..................... 36 years
- did your family have a cat or dog in the home? ... 37 years

How many of the first 15 years of your life
- did you live in a town/city? ..................... 32 years
- did your family have a cat or dog in the home? ... 34 years
### SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you cough about daily for some periods of the year?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If &quot;Yes&quot;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is your cough productive?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you had this kind of cough for as long as 3 months in each of the last two years?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you had episodes of wheezing in your chest?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If &quot;Yes&quot;, has this occurred:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tick one box only for each item.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At night</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>In connection with respiratory infections</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>In connection with physical exertion</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>In connection with very cold weather</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you noticed sudden changes in your pulse or heart rhythm in the last year?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>How often do you suffer from sleeplessness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, or just a few times a year</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>1-2 times a month</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Approximately once a week</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>More than once a week</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If you suffer from sleeplessness, what time of the year does it affect you most?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No particular time of year</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Especially during the polar night</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Especially during the midnight sun season</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Especially in spring and autumn</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you in the last year suffered from sleeplessness to the extent that it has affected your ability to work?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>How often do you suffer from headaches?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely or never</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Once or more a month</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Once or more a week</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Daily</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Does the thought of getting a serious illness ever worry you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Only a little</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Some</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Very much</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### USE OF HEALTH SERVICES

<table>
<thead>
<tr>
<th>Service</th>
<th>Number of times the past year</th>
</tr>
</thead>
<tbody>
<tr>
<td>To a general practitioner (GP)/Emergency GP</td>
<td>191</td>
</tr>
<tr>
<td>To a psychologist or psychiatrist</td>
<td></td>
</tr>
<tr>
<td>To an other medical specialist (not at a hospital)</td>
<td></td>
</tr>
<tr>
<td>To a hospital out-patient clinic</td>
<td></td>
</tr>
<tr>
<td>Admitted to a hospital</td>
<td></td>
</tr>
<tr>
<td>To a medical officer at work</td>
<td></td>
</tr>
<tr>
<td>To a physiotherapist</td>
<td></td>
</tr>
<tr>
<td>To a chiropractor</td>
<td></td>
</tr>
<tr>
<td>To an acupuncturist</td>
<td></td>
</tr>
<tr>
<td>To a dentist</td>
<td></td>
</tr>
<tr>
<td>To an alternative practitioner (homeopath, foot zone therapist, etc.)</td>
<td></td>
</tr>
<tr>
<td>To a healer, faith healer, clairvoyant</td>
<td></td>
</tr>
</tbody>
</table>

### ILLNESS IN THE FAMILY

<table>
<thead>
<tr>
<th>Illness</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Migraine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Fibromyalgia/fibrositis/chronic pain syndrome</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Psychological problems for which you have sought help</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Liver disease</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Allergy and hypersensitivity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic eczema (e.g. childhood eczema)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hand eczema</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hay fever</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Food allergy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other hypersensitivity (not allergy)</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### YOUR OWN ILLNESSES

<table>
<thead>
<tr>
<th>Illness</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Wrist/forearm fracture</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Whiplash</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Injury requiring hospital admission</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gastric/duodenal ulcer surgery</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Neck surgery</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Have you had this in the last 14 days? | ☐ | ☐ |

Needed additional information about symptoms and health services, please refer to the original document for more details.
### MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.

*Put 0 for items you have not used.*

**Medicines**

<table>
<thead>
<tr>
<th>Item</th>
<th>No. of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painkillers</td>
<td>215</td>
</tr>
<tr>
<td>Sleeping pills</td>
<td></td>
</tr>
<tr>
<td>Tranquilizers</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>231</td>
</tr>
<tr>
<td>Allergy drugs</td>
<td></td>
</tr>
<tr>
<td>Asthma drugs</td>
<td></td>
</tr>
</tbody>
</table>

**Dietary supplements**

<table>
<thead>
<tr>
<th>Item</th>
<th>No. of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron tablets</td>
<td>227</td>
</tr>
<tr>
<td>Calcium tablets or bonemeal</td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td></td>
</tr>
<tr>
<td>Other vitamin supplements</td>
<td>233</td>
</tr>
<tr>
<td>Cod liver oil or fish oil capsules</td>
<td></td>
</tr>
</tbody>
</table>

Have you in the last 14 days used the following medicines or dietary supplements?

*Tick one box only for each item.*

**Medicines**

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painkillers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipyretics (to reduce fever)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema cream/ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart medicines (not blood pressure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquilizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other drugs for nervous conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs for hypothyroidism (Thyroxine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other medicine(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dietary supplements**

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium tablets or bonemeal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vitamin supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod liver oil or fish oil capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FOOD HABITS

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (10-12g)

A catering portion is enough for about ___ slices

What kind of fat is normally used in cooking (not on the bread) in your home?

- Butter
- Hard margarine
- Soft margarine
- Butter/margarine blend
- Oils

What kind of bread (bought or home-made) do you usually eat?

*Tick one or two boxes!*

The bread I eat is most similar to:

- Wholemeal bread
- Brown bread
- Rye bread
- White bread
- Leavened bread
- Wholemeal bread

How much (in number of glasses, cups, potatoes or slices) do you usually eat or drink daily of the following foodstuffs?

*Tick one box for each foodstuff.*

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full milk (ordinary or curdled) (glasses)</td>
<td>0</td>
</tr>
<tr>
<td>Semi-skimmed milk (ordinary or curdled) (glasses)</td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (ordinary or curdled) (glasses)</td>
<td></td>
</tr>
<tr>
<td>Tea (cups)</td>
<td></td>
</tr>
<tr>
<td>Orange juice (glasses)</td>
<td></td>
</tr>
<tr>
<td>Potatoes</td>
<td></td>
</tr>
<tr>
<td>Slices of bread in total</td>
<td></td>
</tr>
<tr>
<td>Potatoes in cooking</td>
<td></td>
</tr>
<tr>
<td>Potatoes in other sweet spreads</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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</tbody>
</table>

**FRIENDS**

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? ___ friends

*Do not count people you live with, but do include other relatives!*

How many of these good friends do you have contact with at least once a month? ___

Do you feel you have enough good friends? ___

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ___
- 1-2 times a month ___
- Approximately once a week ___
- More than once a week ___

**FOOD HABITS**

<table>
<thead>
<tr>
<th>Item</th>
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</tr>
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<tbody>
<tr>
<td>Yoghurt</td>
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- Never, or just a few times a year ___
- 1-2 times a month ___
- Approximately once a week ___
- More than once a week ___

**FOOD HABITS**

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (10-12g)

A catering portion is enough for about ___ slices

What kind of fat is normally used in cooking (not on the bread) in your home?

- Butter
- Hard margarine
- Soft margarine
- Butter/margarine blend
- Oils

What kind of bread (bought or home-made) do you usually eat?

*Tick one or two boxes!*

The bread I eat is most similar to:

- Wholemeal bread
- Brown bread
- Rye bread
- White bread
- Leavened bread
- Wholemeal bread

How much (in number of glasses, cups, potatoes or slices) do you usually eat or drink daily of the following foodstuffs?

*Tick one box for each foodstuff.*

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full milk (ordinary or curdled) (glasses)</td>
<td>0</td>
</tr>
<tr>
<td>Semi-skimmed milk (ordinary or curdled) (glasses)</td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (ordinary or curdled) (glasses)</td>
<td></td>
</tr>
<tr>
<td>Tea (cups)</td>
<td></td>
</tr>
<tr>
<td>Orange juice (glasses)</td>
<td></td>
</tr>
<tr>
<td>Potatoes</td>
<td></td>
</tr>
<tr>
<td>Slices of bread in total</td>
<td></td>
</tr>
<tr>
<td>Potatoes in cooking</td>
<td></td>
</tr>
<tr>
<td>Potatoes in other sweet spreads</td>
<td></td>
</tr>
</tbody>
</table>

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</tbody>
</table>
### ALCOHOL

<table>
<thead>
<tr>
<th>How often do you usually drink beer?</th>
<th>wine?</th>
<th>spirits?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never, or just a few times a year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 times a month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>About once a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3 times a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More or less daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?
- Not at all the last year
- A few times
- 1-2 times a month
- 1-2 times a week
- 3 or more times a week

For approximately how many years has your alcohol consumption been as you described above? 312 years

### WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? Write 0 if you never have.
- before age 20
- later

If you have lost weight deliberately, about how many kilos have you ever lost at the most?
- before age 20
- later

What weight would you be satisfied with (your "ideal weight")?

### TO BE ANSWERED BY WOMEN ONLY

#### MENSTRUATION

How old were you when you started menstruating? 328 years

If you no longer menstruate, how old were you when you stopped menstruating? 328 years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more?
- Yes
- No

If "Yes", how many times? 331 times

If you still menstruate or are pregnant:

- day/month/year

Do you usually use painkillers to relieve period pains?
- Yes
- No

#### PREGNANCY

How many children have you given birth to? 349 children

Are you pregnant at the moment?
- Yes
- No
- Don't know

Have you during pregnancy had high blood pressure and/or proteinuria?
- Yes
- No

If "Yes", during which pregnancy?
- First
- Later

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child.

<table>
<thead>
<tr>
<th>Child</th>
<th>Year of birth:</th>
<th>Number of months breastfed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>348</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>356</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>364</td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### URINARY INCONTINENCE

How often do you suffer from urinary incontinence?
- Never
- Not more than once a month
- Two or more times a month
- Once a week or more

Your comments:

#### CONTRACEPTION AND ESTROGEN

Do you use, or have you ever used:
- Oral contraceptive pills (incl. minipill)
- Hormonal intrauterine device
- Estrogen (tablets or patches)
- Estrogen (cream or suppositories)

If you use oral contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?

If you use or have ever used oral contraceptive pills:
- Age when you started to take the pill?
- How many years in total have you taken the pill?
- If you have given birth, how many years did you take the pill before your first delivery?
- If you have stopped taking the pill:
- Age when you stopped?

Thank you for the help! Remember to mail the form today!
The Tromsø Health Survey
**Tromsø Health Survey**

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. Finally, the survey should give knowledge about the older part of the population. We would therefore like you to answer the questions below.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

---

**HOME**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who do you live with?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tick once for each item and give the number.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse/partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other people over 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People under 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What type of house do you live in?</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Villa/ detached house</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Farm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat/apartment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terraced/ semi-detached house</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long have you lived in your present home?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td></td>
<td></td>
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</tbody>
</table>

Is your home adapted to your needs?                                     |     |    |        |

If "No", do you have problems with:                                     |     |    |        |
| Living space                                                           |     |    |        |
| Variable temperature, too cold/too warm                               |     |    |        |
| Stairs                                                                 |     |    |        |
| Toilet                                                                 |     |    |        |
| Bath/shower                                                            |     |    |        |
| Maintenance                                                            |     |    |        |
| Other (please specify)                                                 |     |    |        |

Would you like to move into a retirement home?                           |     |    |        |

---

**PREVIOUS WORK AND FINANCIAL SITUATION**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>How will you describe the type of work you had for the last 5-10 years before you retired?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mostly sedentary work?</td>
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<tr>
<td>(e.g. office work, mounting)</td>
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</tr>
<tr>
<td>Work that requires a lot of walking?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. shop assistant, housewife, teaching)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work that requires a lot of walking and lifting?</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(e.g. postman, nurse, construction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy manual work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. forestry, heavy farm-work, heavy construction)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Did you do any of the following jobs (full-time or part-time)?     |     |    |        |
| Tick one box only for each item.                                       |     |    |        |
| Driver                                                                 |     |    |        |
| Farmer                                                                 |     |    |        |
| Fisherman                                                              |     |    |        |

How old were you when you retired?                                     |     |    |        |

What kind of pension do you have?                                       |     |    |        |
| Basic state pension                                                    |     |    |        |
| An additional pension                                                  |     |    |        |

How is your current financial situation?                                |     |    |        |
| Very good                                                              |     |    |        |
| Good                                                                   |     |    |        |
| Difficult                                                              |     |    |        |
| Very difficult                                                         |     |    |        |

---

**CHILDHOOD/YOUTH**

In which Norwegian municipality did you live at the age of 1 year?      |     |    |        |

If you did not live in Norway, give country instead of municipality

How was your family's financial situation during your childhood?       |     |    |        |
| Very good                                                             |     |    |        |
| Good                                                                   |     |    |        |
| Difficult                                                             |     |    |        |
| Very difficult                                                        |     |    |        |

How old were your parents when they died?                              |     |    |        |
| Mother                                                                 |     |    |        |
| Father                                                                 |     |    |        |
## HEALTH AND ILLNESS

Has your state of health changed in the last year?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, it has got worse ......................</td>
<td>☐ 1</td>
<td>82</td>
</tr>
<tr>
<td>No, unchanged ...................................</td>
<td>☐</td>
<td>2</td>
</tr>
<tr>
<td>Yes, it has got better ......................</td>
<td>☐</td>
<td>3</td>
</tr>
</tbody>
</table>

How do you feel your health is now compared to others of your age?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much worse .....................................</td>
<td>☐ 1</td>
<td>82</td>
</tr>
<tr>
<td>A little worse .................................</td>
<td>☐</td>
<td>2</td>
</tr>
<tr>
<td>About the same ..................................</td>
<td>☐</td>
<td>3</td>
</tr>
<tr>
<td>A little better ..................................</td>
<td>☐</td>
<td>4</td>
</tr>
<tr>
<td>Much better .....................................</td>
<td>☐</td>
<td>5</td>
</tr>
</tbody>
</table>

## YOUR OWN ILLNESSES

Have you ever had:

**Tick one box only for each item. Give your age at the time.**

- Hip fracture .................................................. | ☐ 1 |
- Wrist/forearm fracture ................................. | ☐ | 2 |
- Whiplash .................................................. | ☐ | 3 |
- Injury requiring hospital admission .................. | ☐ | 4 |
- Gastric ulcer .............................................. | ☐ | 5 |
- Duodenal ulcer ............................................ | ☐ | 6 |
- Gastric/duodenal ulcer surgery ....................... | ☐ | 7 |
- Neck surgery ................................................ | ☐ | 8 |

Have you ever had, or do you have:

**Tick one box only for each item.**

- Cancer .......................................................... | ☐ 1 |
- Epilepsy .......................................................... | ☐ | 2 |
- Migraine .......................................................... | ☐ | 3 |
- Parkinson’s disease .......................................... | ☐ | 4 |
- Chronic bronchitis .......................................... | ☐ | 5 |
- Psoriasis .......................................................... | ☐ | 6 |
- Osteoporosis ................................................... | ☐ | 7 |
- Fibromyalgia/fibrositis/chronic pain syndrome .... | ☐ | 8 |
- Psychological problems for which you have sought help | ☐ | 9 |
- Thyroid disease ............................................. | ☐ | 10 |
- Liver disease .................................................. | ☐ | 11 |
- Recurrent urinary incontinence ......................... | ☐ | 12 |
- Glaucoma .......................................................... | ☐ | 13 |
- Cataract .......................................................... | ☐ | 14 |
- Arthrosis (osteoarthritis) .................................. | ☐ | 15 |
- Rheumatoid arthritis ........................................ | ☐ | 16 |
- Kidney stones ................................................... | ☐ | 17 |
- Appendectomy .................................................. | ☐ | 18 |
- Allergy and hypersensitivity .......................... | ☐ | 19 |
  - Atopic eczema (e.g. childhood eczema) ........ | ☐ | 20 |
  - Hand eczema .................................................. | ☐ | 21 |
  - Hay fever ...................................................... | ☐ | 22 |
  - Food allergy .................................................. | ☐ | 23 |
  - Other hypersensitivity (not allergy) ............. | ☐ | 24 |

How many times have you had a common cold, influenza (flu), diarrhoea/vomiting or similar in the last 6 months? 111 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

Have you had this in the last 14 days? 113 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

## ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:

**Tick “None” if none of your relatives have had the disease.**

- Cerebral stroke or brain haemorrhage .......................... | ☐ 1 |
- Heart attack before age 60 ....................................... | ☐ | 2 |
- Cancer ..................................................................... | ☐ | 3 |
- Hyperthyroidism .................................................... | ☐ | 4 |
- Hypertension .......................................................... | ☐ | 5 |
- Asthma ...................................................................... | ☐ | 6 |
- Osteoporosis ............................................................ | ☐ | 7 |
- Arthrosis (osteoarthritis) ..................................... | ☐ | 8 |
- Psychological problems .......................................... | ☐ | 9 |
- Dementia ................................................................. | ☐ | 10 |
- Diabetes ................................................................. | ☐ | 11 |
- - age when they got diabetes .................................................. | ☐ 12|

## SYMPTOMS

Do you cough about daily for some periods of the year? 184 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

If “Yes”:

- Is your cough productive? ........................................... | ☐ | 187 |

Have you had this kind of cough for as long as 3 months in each of the last two years? 188 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

Have you had episodes with wheezing in your chest? 186 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

If “Yes”, has this occurred:

**Tick one box only for each item.**

- At night ................................................................. | ☐ | 189 |
- In connection with respiratory infections .................. | ☐ | 190 |
- In connection with physical exertion ....................... | ☐ | 191 |
- In connection with very cold weather ...................... | ☐ | 192 |

Have you noticed sudden changes in your pulse or heart rhythm in the last year? 190 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

If “Yes”:

- How many kilograms? ................................................ | ☐ 210 |

How often do you suffer from sleeplessness?

- Never, or just a few times a year .......................... | ☐ 1 |
- 1-2 times a month ................................................ | ☐ 2 |
- Approximately once a week ................................... | ☐ 3 |
- More than once a week ......................................... | ☐ 4 |

If you suffer from sleeplessness, what time of the year does it affect you most?

- No particular time of year .................................. | ☐ 1 |
- Especially during the polar night ......................... | ☐ 2 |
- Especially during the midnight sun season ............ | ☐ 3 |
- Especially in spring and autumn .......................... | ☐ 4 |

Do you usually take a nap during the day? 189 times

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>☐</td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

Do you feel that you usually get enough sleep?

<table>
<thead>
<tr>
<th>No</th>
<th>A little</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
</tbody>
</table>

Do you suffer from:

- Dizziness .......................................................... | ☐ 100 |
- Poor memory ....................................................... | ☐ 101 |
- Lack of energy ...................................................... | ☐ 102 |
- Constipation ....................................................... | ☐ 103 |
### BODILY FUNCTIONS

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>With some help</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking indoors on one level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking up/down stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking outdoors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking approx. 500 metres</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Going to the toilet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washing yourself</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking a bath/shower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing and undressing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting in and out of bed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doing light housework (e.g. washing up)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doing heavier housework (e.g. cleaning floor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go shopping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take the bus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MEDICATION AND DIETARY SUPPLEMENTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Put 0 for items you have not used.</th>
<th>Put 0 if you have not had such contact</th>
<th>Number of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painkillers</td>
<td></td>
<td></td>
<td>259 mths</td>
</tr>
<tr>
<td>Sleeping pills</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquilizers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart medicines (not blood pressure)</td>
<td></td>
<td></td>
<td>271 mths</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs for hypothyroidism (Thyroxine)</td>
<td></td>
<td></td>
<td>377 mths</td>
</tr>
<tr>
<td>Cortisone tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remedies for constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary supplements:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron tablets</td>
<td></td>
<td></td>
<td>283 mths</td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vitamin supplements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium tablets or bone meal</td>
<td></td>
<td></td>
<td>289 mths</td>
</tr>
<tr>
<td>Cod liver oil or fish oil capsules</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### USE OF HEALTH SERVICES

<table>
<thead>
<tr>
<th>Health Service</th>
<th>Put 0 if you have not had such contact</th>
<th>Number of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>To a general practitioner (GP)/emergency GP</td>
<td></td>
<td>238 mths</td>
</tr>
<tr>
<td>To a psychologist or psychiatrist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To an other medical specialist (not at a hospital)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a hospital out-patient clinic</td>
<td></td>
<td>234 mths</td>
</tr>
<tr>
<td>Admitted to a hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a physiotherapist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a chiropractor</td>
<td></td>
<td>249 mths</td>
</tr>
<tr>
<td>To a acupuncturist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a dentist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a chiropod</td>
<td></td>
<td>246 mths</td>
</tr>
<tr>
<td>To an alternative practitioner (homeopath, foot zone therapist, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To a healer, faith healer, clairvoyant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FAMILY AND FRIENDS

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Put 0 if you have not had such contact</th>
<th>Number of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close relatives who can give you help and support when you need it?</td>
<td></td>
<td>233 mths</td>
</tr>
<tr>
<td>If &quot;Yes&quot;, who can give you help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse/partner</td>
<td></td>
<td>294 mths</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| How many good friends do you have whom you can talk confidentially with and who give you good help when you need it? | 297 mths |

### Do not count people you live with, but do include other relatives!

<table>
<thead>
<tr>
<th>Good sense of belonging</th>
<th>Put 0 if you have not had such contact</th>
<th>Number of months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong sense of belonging</td>
<td></td>
<td>300 mths</td>
</tr>
<tr>
<td>Some sense of belonging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not sure</td>
<td></td>
<td>297 mths</td>
</tr>
</tbody>
</table>

| Little or no sense of belonging               |                                        |                 |

###OTHERS

- Don't count people you live with, but do include other relatives!
- Do you feel you have enough good friends?
How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ........................................ 1
- 1-2 times a month ................................................................. 2
- Approximately once a week .................................................. 3
- More than once a week .......................................................... 4

**FOOD HABITS**

How many meals a day do you normally eat (dinner and bread meals)? ............................................................... 302

How many times a week do you eat warm dinner? ............................................................... 304

What kind of bread (bought or home-made) do you usually eat?

<table>
<thead>
<tr>
<th>Bread Type</th>
<th>Ticks</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td></td>
</tr>
<tr>
<td>Textured</td>
<td></td>
</tr>
<tr>
<td>Ordinary</td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td></td>
</tr>
<tr>
<td>Coarse</td>
<td></td>
</tr>
</tbody>
</table>

The bread type is most similar to: ............................................................... 306

What kind of fat is normally used in cooking (not on the bread) in your home?

- Butter ........................................................................ 311
- Hard margarine ............................................................. 312
- Soft margarine .............................................................. 313
- Butter/margarine blend .................................................. 314
- Oils ............................................................................ 315

How much (in number of glasses, cups, potatoes or slices) do you usually eat/drink daily the following foodstuffs?

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>None</th>
<th>Less than 1</th>
<th>1-2</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk of all types (glasses)</td>
<td>316</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange juice (glasses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potatoes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slices of bread in total (incl. crispbread)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slices of bread with - fish (e.g. mackerel in tomato sauce)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cheese (e.g. Gouda/Norvegia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- smoked cod caviare</td>
<td>322</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

How many times per week do you normally eat the following foodstuffs?

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>Never</th>
<th>Less than 1</th>
<th>1</th>
<th>2 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoghurt</td>
<td>333</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boiled or fried egg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast cereal/oatmeal, etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinner with - unprocessed meat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- fatty fish (e.g. salmon/red-fish)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- lean fish (e.g. cod)</td>
<td>328</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vegetables (fresh or cooked)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrots (fresh or cooked)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cauliflower/cabbage/broccoli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apples/pears</td>
<td>333</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Oranges, mandarins, etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Your comments:

Thank you for the help! Remember to mail the form today!

Tromsø Health Survey
The health study in Tromsø invites some of the participants for a free special study.

The Special Study involves

- **Ultrasound of blood vessels and the heart**
  The arteries in the neck and stomach are studied. This gives information whether the arteries are clogged or whether they are dilated/contracted. The shape of the heart and its functionality is looked at in 50 per cent of the participants.

- **Study of bone density and amount of fat**
  The measurements are used to determine risks of osteoporosis and fractures, and whether there is a correlation between body fat and disease.

- **ECG**
  ECG is registering heart activity which also provides information concerning heart disease.

- **Urine sample**
  The urine samples are used to indicate kidney function through measuring the amount of protein and creatinine substances. The result is most accurate if urine from the separate days are examined.

- **Blood sample**
  Blood samples are examined for fatty substances and substances which indicate how the kidneys work, metabolism (calcium and sugar) and blood clotting. The blood sample is frozen so it can be used for later research.

Further follow up

- If we think further examination or treatment is required, it will be offered to you.
- Some participants may be asked to take part in later studies for further research.

Practical information

**Place and time**
The examination will take place in the second floor at Elisabeth center: the old maternity hospital (Mellomveien 50) - at the floor above the Tromsø study. The examination takes 1 to 1.5 hours and is free of charge.

We hope you can use the time appointed. Date and time is given in the brochure. If you need to change appointment, we ask that you notify us by calling 77 64 59 00.

**Urine sample**
You have been given three urine glasses marked 1, 2 and 3. We wish that you take a morning urine sample in each glass in the last three days before the special study. You have therefore got a glass for every morning. Note the following:

1. Please urinate a small amount of urine in the toilet before you take the urine sample. Last morning sample is taken on the day you come to the survey.
2. State the date on each urine glass.
3. It is an advantage if samples can stay cold.
4. Deliver all three glasses when you come to the survey.

**Use of medicine**
On the next page please make a note which medications you've used the past week. This can be important when interpreting the results.

**Clothing**
Because of the blood pressure measuring, we ask you to wear clothes that are not tight on the arm. When examining the heart, it is necessary to undress the upper body. At examination of the aorta some clothes must be pulled down so that the abdominal region is exposed.
About consent

The information about you will be treated confidentially. The information will be stored and used according to the rules set by the Data Inspectorate and Norwegian law. The study has been recommended by The Regional Committee for Research Ethics. Should further examinations be required, we ask your consent to forward relevant data to your doctor or the Regional Hospital in Tromsø. We also request that you upon arrival give your consent to:

- that we forward your results to your doctor or the Regional Hospital in Tromsø if you need further examination.
- that your results may be used for medical research through combining them with other health- and disease registries as well as information from previous health studies in Tromsø. Prior to analysing the results your name and social security number will be removed.
- that your blood sample may be stored and used for medical research.
- that the Health Examination in Tromsø may contact you later with a request to participate in other studies.

Even if you give your consent now, you may later reconsider and deny the use of your results.

The special study

is part of the health survey in Tromsø, and organized by the University of Tromsø, Faculty of Medicine in cooperation with the Regional Hospital in Tromsø

Use of medicine

To interpret the results we want information about medication use in the last week. Please state name, strength and dose of all medications that you are using. If in doubt about filling, bring the drugs. We will then be able to help you.

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Strength</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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