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Lifestyle factors and risk of venous thromboembolism

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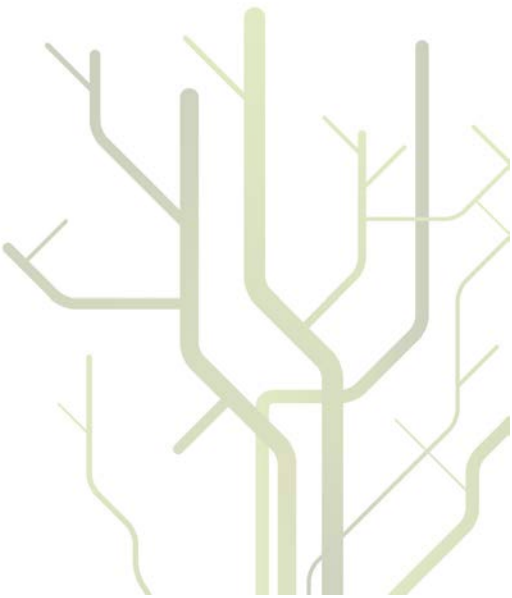

CONTENTS

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SUMMARY

There is little knowledge about the association between lifestyle factors and risk of venous thromboembolism (VTE). The aim of this thesis was to investigate the relation between coffee consumption, emotional states, cigarette smoking and socioeconomic status and future risk of incident VTE in a prospective, population-based cohort study.

Our study population consisted of more than 27 000 men and women, who participated in the fourth Tromsø study (1994-95). All adult inhabitants of the municipality of Tromsø, Norway, were invited to participate in the Tromsø study. Information about lifestyle factors and other relevant factors, were obtained by self-administered questionnaires, blood samples and a physical examination. The study subjects were followed until end of follow-up, December 31, 2010, and all VTE events occurring during this time period were registered.

We found that coffee consumption was inversely associated with risk of VTE. Subjects who drank 3-6 cups of coffee daily had about 30% lower risk of VTE than coffee abstainers. Subjects who reported frequent feelings of depression in the 2 weeks prior to baseline had 60% higher risk of VTE compared to those who reported no such feelings. Contrary, those who felt happy and optimistic had 40% reduced risk of VTE. Heavy smoking was apparently associated with risk of VTE, but this association was mediated by other smoking-attributable diseases, such as myocardial infarction and cancer. Furthermore, women with high socioeconomic status had lower risk of VTE than women with low socioeconomic status. No association between socioeconomic status and risk of VTE was found among men. These findings imply that lifestyle factors have impact on the risk of VTE.

SAMMENDRAG

Det er begrenset kunnskap om assosiasjonen mellom livsstilsfaktorer og risikoen for venøs tromboembolisme (VTE). Hensikten med denne avhandlingen var å studere sammenhengen mellom kaffekonsum, sinnsstemninger, røyking og sosioøkonomisk status og risikoen for førstegangs VTE i en prospektiv, populasjonsbasert kohortestudie.

Studien tok utgangspunkt i den fjerde Tromsøundersøkelsen (1994-95) der mer enn 27 000 menn og kvinner deltok. Alle personer over 25 år som bodde i Tromsø kommune var invitert til å delta i Tromsøundersøkelsen. Informasjon om livsstilsfaktorer og andre faktorer av betydning, ble samlet inn ved hjelp av spørreskjema, blodprøver og en klinisk undersøkelse. Personene ble fulgt frem 31. desember 2010, der alle VTE-hendelser i denne perioden ble registrert.

Vi fant at kaffekonsum var inverst assosiert med risiko for VTE. Personer som drakk 3-6 kopper kaffe daglig hadde omtrent 30% lavere risiko for VTE sammenliknet med personer som ikke drakk kaffe. Personer som oppgav at de ofte hadde følt seg deprimert og nedfor de siste to ukene før studiedeltakelse hadde 60% høyere risiko for VTE sammenliknet med dem som ikke følte seg deprimerte. På den andre siden, hadde personer som følte seg glade og optimistiske 40% redusert risiko for VTE. Det å røyke mye var assosiert med økt risiko for VTE, men det viste seg at det skyldtes andre røyke-relaterte sykdommer som hjerteinfarkt og kreft. Videre fant vi at kvinner med høy sosioøkonomisk status hadde lavere risiko for VTE enn kvinner med lav sosioøkonomisk status. Det var ingen assosiasjon mellom sosioøkonomisk status og VTE blant menn. Våre funn tyder på at livsstil har vesentlig betydning for forekomsten av VTE i befolkningen.

LIST OF PAPERS

The thesis in based on the following papers:

I. Coffee consumption and the risk of venous thromboembolism. The Tromsø study.

Enga KF, Braekkan SK, Hansen-Krone IJ, Wilsgaard T, Hansen JB.

J Thromb Haemost. 2011;9(7):1334-9.

II. Emotional states and future risk of venous thromboembolism: the Tromsø Study.

Enga KF, Brækkan SK, Hansen-Krone IJ, Hansen JB.

Thromb Haemost. 2012;107(3):485-93.

III. Cigarette smoking and the risk of venous thromboembolism: the Tromsø Study.

Enga KF, Braekkan SK, Hansen-Krone IJ, le Cessie S, Rosendaal FR, Hansen JB.

J Thromb Haemost. 2012;10(10):2068-74.

IV. Socioeconomic status and the risk of venous thromboembolism – The Tromsø study

Enga KF, Braekkan SK, Skjeldestad FE, Hansen JB.

Submitted.

ABBREVIATIONS

APC – Activated protein C

aPTT - Activated partial thromboplastin time

BMI – Body mass index

CAD – Coronary artery disease

CCHS – Copenhagen City Heart Study

CI – Confidence intervals

COC – Combined oral contraceptives

COPD – Chronic obstructive pulmonary disease

CRP – C-reactive protein

CT – Computed tomography

CVD – Cardiovascular disease

DCH – Diet, Cancer and Health study

DVT – Deep vein thrombosis

FV – Factor V

FVa – activated factor V

FVII – Factor VII

FVIII – Factor VIII

VIII:C – Factor VIII coagulant activity

FXII:C – Factor XII coagulant activity

GWAS - Genome wide association study

HC – Hip circumference

HDL – High density lipoprotein

HR – Hazard ratio

HRT – Hormone replacement therapy

Hs-CRP – High-sensitivity C-reactive protein

HUNT – Helseundersøkelsen i Nord-Trøndelag

ICD – International classification of diseases

IU/L – International units per litre

IWHS - The Iowa Women's Health Study

LCI - Living Condition Index

LDL – Low density lipoprotein

LITE-study - Longitudinal Investigation of Thromboembolism Etiology study

MAR – missing at random

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

MI – Myocardial infarction

MISS-study - Melanoma Inquiry of Southern Sweden study

OC – Oral contraceptives

OR – Odds ratio

PAI-1 - Plasminogen activator inhibitor-1

PE – Pulmonary embolism

RCT – Randomized controlled trial

SCI – Socioeconomic condition index

SES – Socioeconomic status

SNP – Single nukleotide polymorphism

TF – Tissue factor

t-PA - Tissue plasminogen activator

US – United states of America

VTE – Venous thromboembolism

VWF – Von Willebrand Factor

WC – Waist circumference

1. INTRODUCTION

1.1 Pathophysiology of venous thromboembolism

Venous thromboembolism (VTE) is defined as deep vein thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis is blood clots most commonly occurring in the deep veins of the lower extremities. A part breaking free from the blood clot, and transported by the circulation to the arteries of the lungs, is pulmonary embolism. In 1856, Rudolph Virchow postulated three major contributors to the pathophysiology of thrombosis: changes of blood composition, alterations in the blood flow and changes of the vessel walls (figure 1). These factors still apply, but the understanding of the pathogenesis of venous thrombosis has expanded. Arterial thrombi usually occur at sites of high shear stress where atherosclerotic plaques rupture, leading to exposure of subendothelial tissue factor (TF), collagen and von Willebrand factor (VWF) [1, 2]. These thrombi are platelet-rich and are therefore called white thrombi [2]. Venous thrombi, on the other hand, are called red thrombi as they have a body of fibrin [2], while platelets are attached to the thrombus further from the site of attachment [3]. They usually occur at sites of low shear stress where the endothelium remains intact [4]. The venous valvular sinuses of the calf veins are common locations for the initiation of venous thrombi (figure 2) [4-7]. These sinuses are especially vulnerable to haemoglobin desaturation and hypoxia when blood flow ceases, as blood is trapped in a secondary vortex [7]. The hypoxia

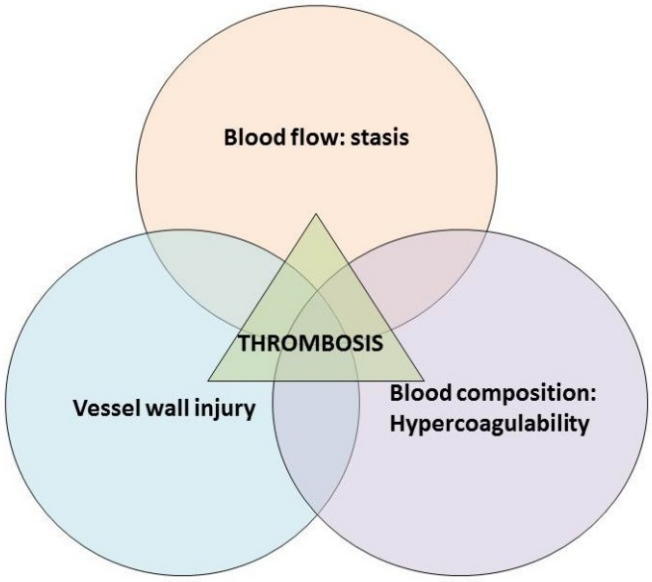

Figure 1. Virchows triad.

caused by blood stasis leads to stimulation of the endothelium resulting in a proinflammatory and prothrombotic state [8-10]. The activated endothelial cells release Weibel-Palade bodies which contain VWF and membrane-bound P-selectin which leads to the binding of leucocytes, TF-positive microparticles and platelets [8-11]. The leucocytes, especially the monocytes, can synthesize and release tissue factor when stimulated [8, 12]. TF from leucocytes and microparticles binds to coagulation factor VIIa and results in activation of the coagulation cascade and initiation of thrombosis [11, 13]. Blood stasis may also lead to accumulation of prothrombotic substances, such as thrombin, which may overcome the local anticoagulant regulators, and may induce thrombosis [14, 15]. Other factors may also contribute to thrombosis. Alterations of blood composition as inherited thrombophilia and acquired factors causing a hypercoagulable state make subjects more susceptible to VTE [16]. We know less about the role of the vessel wall. However, age is the most important risk factor for VTE, and it is postulated that this may be due to stiff valves [17, 18] and reduced compliance of the vein wall [19, 20] which may affect the normal blood flow of the valvular cycle.

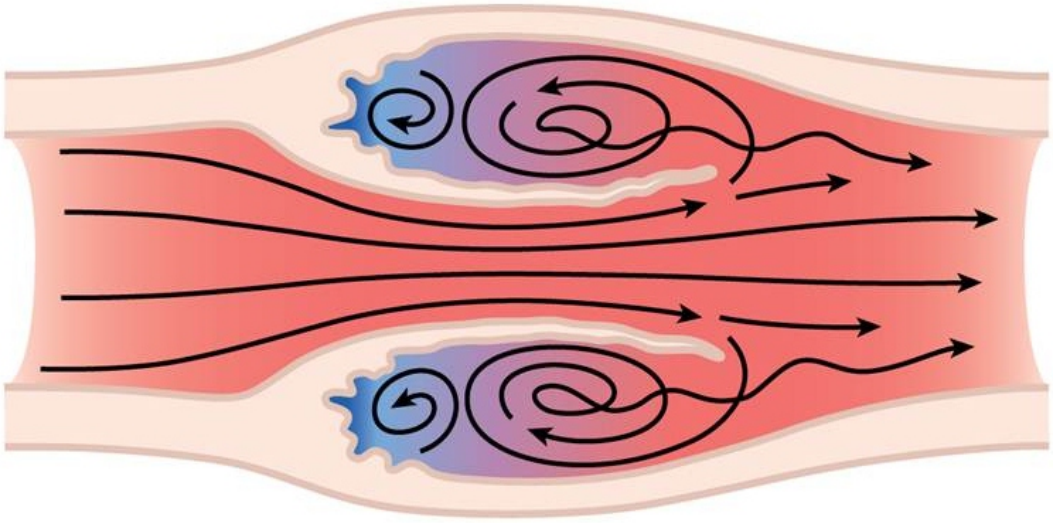

Figure 2. Schematic representation of the vortical flow characteristic of streamlined flow observed in the deep venous system. Oxygen tension is color coded with a gradient from red to blue; the darker the blue is, the greater the hypoxia. The flow arrows define the genesis of the two counterrotating vortices within the valve sinus. The small vortex at the base of the valve sinus is isolated from the systemic circulation and is congruent with the region of most marked hypoxia, which is the usual site of valvular sinus thrombus initiation. An interesting anatomical feature is the small recesses at the base of the sinus. These are evident on histological sections of valves and likely represent microdomains with the greatest degree of stasis and hypoxia and thus candidate loci for thrombus initiation.

1.2 Epidemiology of venous thromboembolism

The annual incidence of VTE is about 1-2 per 1000 individuals in Western countries [21-23], and is the third most common cardiovascular disease after coronary artery disease (CAD) and stroke [24]. About 2/3 of the cases of VTE are DVTs, while the remaining 1/3 are pulmonary embolisms [25]. Typical symptoms of DVTs are pain, swelling, redness and loss of function of the lower extremity, while PE is usually presented as dyspnoea, tachypnoea and pleuritic chest pain [26]. DVT and pulmonary embolism are often present at the same time. Of those presenting with a DVT, 50-80% have concurrent clinical or asymptomatic PE [27]. Other way around, 50-60% of those presenting with PE have positive findings of DVT [28, 29]. Cases of VTE are also divided into provoked and unprovoked events depending on the

circumstances at the time of diagnosis. Provoked VTE events occur in the presence of transient or persistent risk factors, while VTE events with no apparent risk factors present are classified as unprovoked [30]. This classification is of importance in terms of risk of recurrence and treatment duration [30].

VTE is a major source of both morbidity and mortality. A diagnosis of VTE can be complicated by embolization, recurrent episodes, the development of post-thrombotic syndrome and pulmonary hypertension, a complication of pulmonary embolism [27, 31]. Recurrence occurs frequently. About 30% experience a recurrent VTE within 10 years after VTE-diagnosis, and the risk is highest the first 6-12 months [32]. Furthermore, patients with incident PE have 4-fold higher risk of recurrent PE within 6 months compared to patients with DVT [33, 34], while DVT patients have almost 3-fold higher risk of recurrent DVT compared to patients with PE [34]. The risk of recurrence is much higher among those with unprovoked events compared to those with events associated with transient risk factors, such as surgery [35]. Post-thrombotic syndrome is a chronic condition that evolves in at least 1/3 of patients with a diagnosis of DVT, and includes symptoms such as pain and heaviness of limbs, swelling, stasis dermatitis and in severe cases, venous ulcers [36]. VTE is also the leading cause of preventable death in hospitalised patients and the leading cause of maternal death in the US [37]. The case-fatality rate within the first month after diagnosis is about 6% for DVT, near 12% for PE [25], and is even higher for cancer-associated VTE (25%) [23].

1.3 Risk factors for venous thromboembolism

A risk factor is anything that affects the incidence of a disease [38]. Venous thromboembolism is a multifactorial disease where the presence of several factors at the

same time often is necessary for thrombosis to develop [39]. There are many known factors which are associated with the risk of VTE, and they are divided into two major groups: hereditary/genetic risk factors and non-hereditary/environmental risk factors.

1.3.1 Hereditary risk factors

Family- and twin studies have shown that 50-60% of the variation in susceptibility to VTE is attributable to genetic factors [40-42]. To date, some strong and several weak genetic risk factors have been identified. Strong genetic risk factors are deficiencies of antithrombin , protein C and S, activated protein C (APC) resistance, prothrombin 20210A mutation and ABO group [43] with risk estimates varying from 1.5 to 10 [44-48]. **Deficiencies of antithrombin, protein C and S** are relatively rare with a prevalence lower than 1% [49-51], and there are many mutations responsible for these deficiencies [52]. Subjects with protein C deficiency have a 4 to 8-fold increased risk of VTE compared to non-carriers, while those with protein S deficiency and individuals with antithrombin deficiency have a 10-fold increased risk compared to non-carriers [47, 48]. **APC resistance** is in most cases caused by factor V Leiden mutation, which is a point mutation of the factor V gene that leads to the substitution of one amino acid. This makes factor V resistant to activated protein C, which inactivates FVa at a rate 10 times slower than normal [53, 54]. About 5% of the European population are carriers of the mutation, while it is rare in continents as Asia and Africa [55]. Heterozygous carriers have a 3 to 6-fold increased risk compared to non-carriers [46, 56, 57], while homozygous carriers have a much higher risk of VTE [46, 58]. **Prothrombin 20210A** is the substitution of one nucleotide (G to A) in one of the introns of the prothrombin gene, which is regulatory for prothrombin expression, leading to upregulation of gene translation [45]. Hence, carriers have increased concentrations of prothrombin [45]. The mutation is

quite common, with a prevalence of 1-2% of the general population, but it is more common in Europe than in Asia and Africa [59] . The risk of VTE is increased by 2-3 times among carriers compared to non-carriers [45, 60]. **ABO blood group** is a determinant for levels of von Willebrand factor, as those with blood type O have 30% lower VWF levels than other blood types [61]. Consequently, ABO has impact on levels of Factor VIII (FVIII) since VWF is a carrier for FVIII and prevents it from degradation [62]. It has been shown that individuals with non-O blood type have a nearly 2-fold increased risk of VTE compared to those with blood type O [44, 63]. Although the risk estimates are moderate, the population-attributable fraction is substantial due to the prevalence of non-O blood type [44]. Concentrations of **factor VIII** rely on both hereditary and non-hereditary factors, in which 40% of factor VIII coagulant activity (VIII:C) variation is due to genetic factors [64]. High concentrations of FVIII are quite common in the general population and are associated with increased risk of VTE [65, 66]. Those having values exceeding 1500 IU/L have a 6-fold higher risk of VTE compared to those with lower levels (<1000 IU/L) [66]. Several weak risk factors for VTE have been discovered by the genome-wide association studies (GWAS) in which common genetic variations, represented by single nucleotide polymorphisms (SNPs), are investigated in relation to risk of VTE in case-control studies [67]. By GWAS, several alleles from haemostasis-related genes have been identified to be associated with increased or decreased risk of VTE, but the size of the risk estimates is modest (odds ratio (OR) about 0.80-1.20) [68-70]. There are also individuals with combined defects. In general, combined defects yield higher risk of VTE than single defects [39], and interactions are also observed. A pooled analysis of case-control studies found that carriers of factor V Leiden and carriers of prothrombin 20210A mutation had an OR of 4.9 and 3.8, respectively [71]. A multiplicative effect was observed among individuals who had both defects, with an OR of 20 [71].

1.3.2 Non-hereditary risk factors

Examples of non-hereditary risk factors for VTE are advancing age, obesity, chronic disease and cancer. The risk of VTE is highly dependent on age with an incidence ranging from 1/100 000 people per year in childhood [72] to nearly 1% per year in old age [21, 22, 73]. Subjects older than 70 years had 11-fold higher risk of VTE compared to those younger than 50 years participating in the Tromsø study (figure 3) [73]. There may be several reasons why age is an important risk factor for VTE. Both accumulation of risk factors and the biology of aging may play a part. Elderly are more susceptible to immobilization, cancer and other illnesses which are associated with VTE [74]. Aging has been associated with increased levels of fibrinogen, certain coagulation factors, plasminogen activator inhibitor-1 (PAI-1), d-dimer and homocysteine, which are associated with increased risk of VTE [74, 75]. It has also been demonstrated that muscle strength decreases with increasing age, which may affect the muscle pump [76]. In addition, aging is also associated with changes of the vein wall [19, 20] and alterations of venous valves [18, 77]. These factors may result in a disturbed blood flow and potentially lead to thrombus formation.

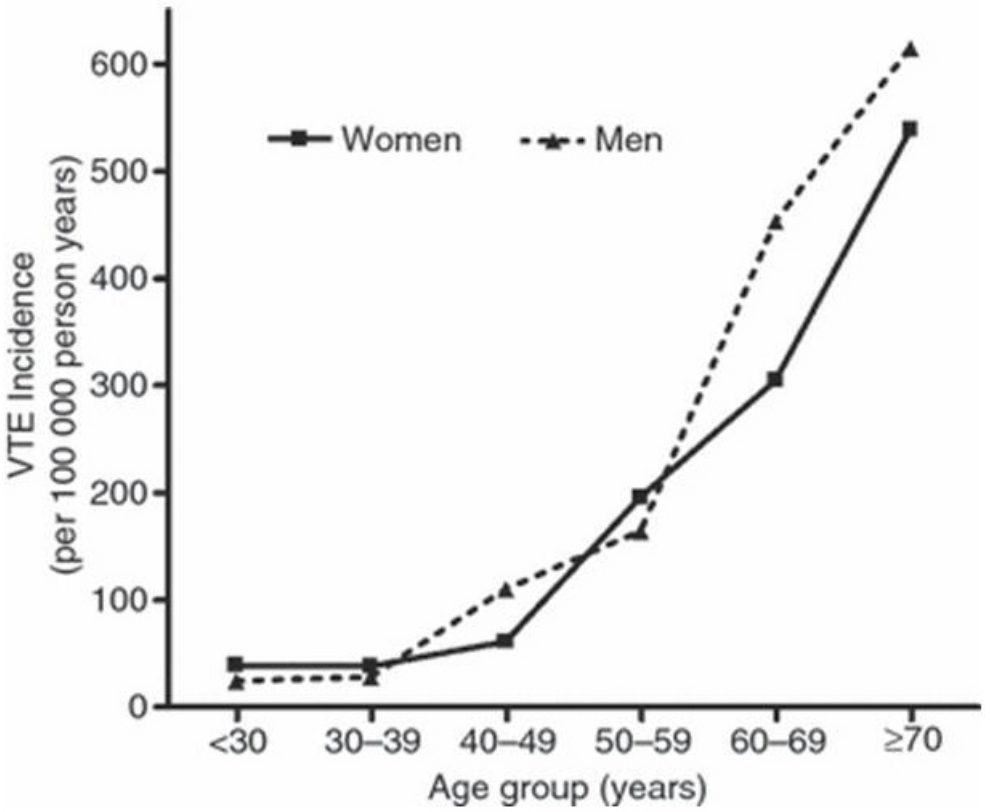

Figure 3. Line graph showing the incidence of VTE in men and women with increasing age.

Obesity is another important risk factor for VTE [24, 73, 78-81]. Results from the Physicians' Health Study showed an even stronger association between increasing body mass index (BMI) and VTE compared to the association between BMI and CAD or stroke [24]. Obesity, defined as BMI ≥30, yields a 2-3-fold higher risk of VTE compared to non-obese [73, 78-80]. The number of obese has increased the last 30 years, with a prevalence of 35% among adults in the US in 2009/2010 [82, 83], whereas the prevalence of overweight (BMI >25-29.99) and obesity in Norway was 33% and 9% in 2009, respectively [84]. This high prevalence of obesity may influence future incidence rates of VTE [85]. To stratify subjects according to risk of VTE, it is essential to find the best anthropometric predictor of VTE risk. The Danish Diet,

Cancer and Health (DCH) study found that all measures of obesity, including BMI, body weight, waist and hip circumference (WC and HC) and fat weight, were associated with increased risk [86]. Results from the Tromsø study showed that WC was the preferred anthropometric predictor of VTE risk compared to other measures due to the highest risk estimates and identification of the highest number of subjects at risk. [87]. A synergistic effect between obesity and body height has also been demonstrated [88]. Adipose tissue is characterized by hyperplasia and hypertrophy of adipocytes, as well as infiltration of macrophages and fibrosis [89]. Obesity is a prothrombotic state, as it is associated with increased platelet aggregation, TF-mediated coagulation, increased levels of fibrinogen and certain coagulation factors, increased PAI-1 which inhibit fibrinolysis, and endothelial dysfunction [85, 90, 91]. These effects could be caused by adipose tissue that synthesize different substances such as PAI-1 directly [92], inflammatory cytokines secreted from adipose tissue that affect haemostatic factors [90], and the secretion of adipokines such as leptin, that have effect on platelet function and TF [91, 93]. In addition, obesity may affect VTE risk mechanically as it has been shown that flow dynamics in the veins of the lower extremities differ between obese and non-obese subjects [94]. In addition, increased intra-abdominal pressure, in terms of pneumoperitoneum during laparoscopic surgery, has been associated with decreased blood flow and increased cross-sectional area of the femoral veins [95].

More than 50% of VTE events are attributed to **institutionalization**, in which 24% are due to surgery, and medical disease account for 22% [96]. Hospitalized patients have 100 times higher risk of VTE compared to community residents [97] as they are exposed to many VTE risk factors, such as infection, surgery, immobility and cancer. Prevention strategies as

thromboprophylaxis in the hospital setting are therefore important to reduce the incidence of VTE in both of these patient groups [96]. **Surgery** and **trauma** are independent risk factors for VTE [98]. A case-control study found a 22-fold increased risk for surgery, whereas trauma was associated with a 12-fold increased risk for asymptomatic VTE [98]. For patients undergoing surgery, the risk of VTE depends on patient age, type of surgical procedure, presence of cancer and other VTE risk factors, duration of surgery and type of anaesthesia [99, 100]. High risk surgical procedures include neurosurgery, hip replacement and major vascular surgery among others [99]. It has been shown that 40-60% of patients undergoing major orthopaedic surgery without thromboprophylaxis developed asymptomatic DVT during the first two weeks after surgery [100]. Using thromboprophylaxis in relation to hip- and knee replacement has reduced the incidence of post-operative asymptomatic DVT to about 20% [101, 102], and symptomatic VTE to about 4% [103]. The risk of VTE is also influenced by type of anaesthesia, in which general anaesthesia is associated with higher risk of VTE compared to use of regional anaesthesia [104, 105]. Medical patients are also susceptible to VTE. **Congestive heart failure** yielded a nearly 3-fold increased risk of VTE in case-control studies [106, 107]. **Chronic kidney disease** is also a risk factor for VTE. Those with stage 3/4 chronic kidney disease have about 50% higher risk compared to those with normal kidney function [108, 109]. **Acute infections** are associated with an 1.5-2-fold higher risk of VTE [106, 110, 111], and other **chronic inflammatory diseases** such as inflammatory bowel disease [112] or rheumatoid arthritis [113], have also been associated with increased risk of VTE. Hospitalized patients with **exacerbation of chronic obstructive pulmonary disease** (COPD) are considered to be at increased risk of VTE due to the presence of other risk factors as immobilization, infections, heart failure and venous stasis [114]. Whether

COPD itself is a risk factor for VTE is not known [106]. In addition, the risk of VTE is increased in the presence of **central venous catheters** and **pacemakers** [98].

As mentioned, the relationship between **immobility** and VTE development is well established [115]. A study of stroke patients with hemiplegia found that 60% developed DVT in their paralyzed leg, while 7% developed DVT in the non-paralyzed leg [116]. Furthermore, neurological disease with extremity paresis has been shown to cause a 3-fold higher risk of VTE [98]. Other types of immobility, such as use of plaster cast or confinement to bed or armchair, are also associated with risk of VTE [106]. A recent case-control study found that even work- and computer-related seated immobility (at least 10 hours during a period of 24 hours and minimum 2 hours continuously in the last 4 weeks prior to VTE event) was associated with risk of VTE, with an OR of 2.8 [117]. Subjects travelling by air exceeding 4 hours as well as travelling by car, bus or train are susceptible to VTE in the following weeks after travel [118]. Based on these findings, it was suggested that the association between air travel and VTE was most likely due to immobilization, and not hypobaric hypoxia, another proposed mechanism for the association. Furthermore, the same study found that tall or low subjects, or those with high BMI, had an even higher risk of VTE after all modes of travel, suggesting that these subjects are even more exposed to immobilization and venous compression during travel [118].

Subjects with cancer and deep vein thrombosis were described by Trousseau already in 1850 and have been a subject for investigation ever since [119]. **Cancer** is now recognised as a major risk factor for VTE as cancer patients have a 4 to 7-fold higher risk of VTE compared to those without malignancy [98, 120, 121]. Yearly, more than 1% of all cancer patients

experience a VTE event [122], and several studies have shown that the incidence of VTE among cancer patients is increasing [123, 124]. Vice versa, active cancer accounts for nearly 20% of all incident VTE events [96]. Patients with unprovoked VTE have increased risk of cancer for at least 2 years after the diagnosis of VTE [125]. Among cancer patients, factors of importance for risk of thrombosis include time after diagnosis, type of cancer, cancer stage and presence of metastases, and cancer treatment [120-122, 126, 127]. The multiple environmental and genetic assessment of risk factors for venous thrombosis-study (MEGA), a case-control study, found that the risk of VTE was highest the first 3 months after diagnosis of cancer [120]. Cancer of the brain and pancreas are among the cancer types with the highest risk of VTE [122], while prostate and breast cancer are cancer types with low risk of VTE [122]. The presence of distant metastases yields a 2-fold higher risk of VTE than cancer patients without metastases [121]. However, it is suggested that VTE risk is linked to tumour growth rate rather than the spread of the tumour [126]. Both surgical and non-surgical cancer therapy are associated with risk of VTE. Cancer patients undergoing surgery have 2 to 4-fold higher risk for postoperative VTE compared to cancer-free surgical patients [99, 128], although there are also studies who did not find any increased risk of VTE in cancer surgery [121, 126]. Use of chemotherapy yields 2-3-fold higher risk of VTE [121, 127]. Other non-surgical therapies, such as use of lenalidomide and thalidomide, antiangiogenic therapy, erythropoietic stimulating agents, and hormonal therapy, are also associated with increased risk of VTE [126, 129]. VTE among cancer patients has impact on both morbidity and mortality. Most importantly, VTE in cancer patients is a predictor of poor survival with a mortality ratio of 2 in cancer patients with VTE compared to cancer patients without VTE [130-132]. VTE in these patients is also associated with a 3-fold higher risk of recurrent VTE and higher risk of complications, such as bleeding due to anticoagulant treatment, compared

to cancer-free patients with incident VTE [133]. In addition, VTE in subjects with cancer leads to long lasting hospitalizations which imply consumption of substantial amounts of health resources [134]. Cancer can potentially affect all components of Virchows triad. Venous stasis can be caused by immobilization or compression of blood vessels by the tumour [135]. Blood components may alter due to the malignancy; many cancer patients have high levels of coagulation factors and proteins involved in fibrinolysis, leading to imbalance of coagulation and fibrinolysis [129]. Cancer cells express high levels of TF and other procoagulants which activate the coagulation system [129]. The malignant cells interact with monocytes, which may lead to release of cytokines that cause endothelial damage, and activation of platelets and coagulation factors, which initiate thrombosis [136]. The endothelial cells may also be damaged by cancer treatments as central venous catheters and chemotherapy [135]. As cancer has impact on the haemostatic system, it is believed that the haemostatic system may also influence the growth and proliferation of the tumour [129].

Use of oestrogens, in terms of combined oral contraceptives (COCs) and hormone replacement therapy (HRT), **pregnancy** and the **post-partum period** are all risk factor for VTE among women. Women using combined oral contraceptives have 3-4-fold higher risk of VTE compared to non-users [137, 138]. The increased risk persists until discontinuation, although the risk is highest the first year of use [137]. The dosage of oestrogens and type of progesterone used in the contraceptive pill, are associated with thrombosis risk. Use of COCs containing high doses of oestrogen (≥50 μg) yields a higher risk of VTE compared to COCs with lower doses of oestrogen (<50 μg) [137]. With regards to type of progesterones and risk of VTE, second generation COCs (containing levonorgestrel, norgestrel and norgestimate) seems to be the safest alternative as third generation COCs (containing desogestrel or

gestodene) are associated with about 60-70% higher risk of VTE compared to use of second generation COCs [137, 139]. Similar findings are also found for fourth generation COCs and antiandrogenic COCs [140]. Use of COCs leads to increase of procoagulants such as FVIII, and decrease of anticoagulants such as protein S [141]. Use of HRT is associated with a 2-3-fold higher risk of VTE, but the absolute risk for women using HRT is higher than for those using oral contraceptives due to their higher age [142, 143]. Pregnancy leads to physiologic changes in the coagulation and fibrinolytic systems, which may be essential to minimize bleeding complications during delivery [144]. Pregnant women have a 4 to 5-fold higher risk of VTE compared to non-pregnant women, and the risk is highest during the third trimester [145-147]. An even higher risk of VTE has been observed in the postpartum period, especially the first weeks after delivery [145-147].

We know many genetic and environmental risk factors for VTE, and the risk of VTE is even greater when individuals are concurrently exposed to several risk factors. Biological interaction refers to the concept that the joint effect of two risk factors on disease occurrence differs from the sum of the individual effect of each risk factor [148]. Such interactions have been observed between factor V Leiden and prothrombin 20210A mutation, and pregnancy [145, 149] and use of oral contraceptives [71, 150]. A case-control study from the Netherlands found that pregnant women with heterozygous FV Leiden and prothrombin 20210A, in comparison with non-pregnant women, had 52-fold and 31-fold higher risk of VTE, respectively [145]. A 34-fold higher risk of VTE has been observed in oral contraceptive (OC) users with FV Leiden mutation, in contrast to OC users with a 4-fold higher risk, and an 8-fold higher risk among FV Leiden carriers, compared to non-users without FV Leiden [150]. Although there are diverging conclusions, interaction of additive

manner has also been observed in some studies investigating FV Leiden and prothrombin 20210A mutation and lifestyle factors, such as obesity and smoking [81, 151, 152].

1.4 The potential relation between arterial cardiovascular disease and venous thromboembolism

VTE and arterial cardiovascular disease (CVD), such as myocardial infarction (MI) and ischaemic stroke, have generally been considered as two distinct entities with different pathophysiology, risk factors and treatment. However, this point of view was challenged when Prandoni and co-workers found that subjects with an event of unprovoked deep vein thrombosis had a higher prevalence of asymptomatic carotid plaques compared to subjects with provoked DVT or hospital controls [153]. Whether atherosclerosis and VTE shared common pathophysiologic pathways or shared common risk factors was questioned, and has been a focus of research ever since. Another case-control study reached similar conclusions when they found an association between coronary artery calcification and subsequent risk of VTE [154], whereas later prospective studies have failed to find an association between subclinical atherosclerosis and VTE risk [155, 156] . Furthermore, several case-control studies have found a higher risk of arterial CVD among those with unprovoked VTE compared to those with provoked VTE [157, 158]. In addition, a higher risk of arterial CVD has been observed among VTE patients compared to controls in a retrospective cohort of VTE patients and randomly selected controls [159], and in a population-based prospective registry study [160]. Other way around, a 25-30% higher risk of VTE was observed in patients with MI and stroke compared to controls in a population-based case-control study [161]. The risk was highest within the first three months after the arterial events [161]. Family history of MI has also been shown to be associated with increased risk of VTE [73, 162]. Whether arterial and

venous thromboses share other risk factors has been investigated in many studies with diverging results. Two prospective cohort studies have studied the association between cardiovascular risk factors, CAD and VTE in the same population, using cause-specific analyses, in which the other outcome was taken into account. Only BMI and age were associated with both VTE and CAD, whereas blood pressure, cholesterol levels, diabetes and smoking were associated with CAD only [24, 163]. Furthermore, arterial CVD and VTE have traditionally been treated differently. However, common features for the treatment of venous and arterial thrombosis have also been shown. Statins, which reduce the blood levels of low density lipoproteins (LDL) used in the prevention of mortality and morbidity of arterial thrombosis, have been reported to reduce the risk of VTE by 20-40% both in observational studies and randomized trials [164-166]. However, a recent meta-analysis of 22 published and unpublished clinical trials found no significant reduced risk of VTE among statin users compared to controls [167]. Aspirin is an antiplatelet drug used in the primary and secondary prevention of arterial thrombosis [168]. Long-term therapy of aspirin has not yielded convincing results in reducing the risk of incident VTE [169], but recent results from randomized trials have shown a 32% reduced risk of recurrent VTE and a 34% lower risk of major vascular events (VTE, MI, stroke or cardiovascular death) after an event of unprovoked VTE for those who were assigned to aspirin after completion of anticoagulation therapy compared to controls using placebo after anticoagulation therapy [170, 171]. The anticoagulants warfarin and heparins are implemented both in the treatment of VTE and arterial CVD [30, 172-174].

1.5 Coffee consumption and the risk of venous thromboembolism

Coffee is one of the most widely consumed beverages worldwide. The beneficial and detrimental effects of coffee consumption on health outcomes have gained considerable attention since the high consumption of coffee may have consequences for public health. Coffee consumption has been inversely associated with overall mortality [175] and various diseases [176], such as diabetes type 2 [177, 178], Parkinson disease [179], Alzheimer's disease [180] and some types of cancers [181]. Results concerning the association between coffee intake and risk of arterial CVD are diverging. Meta-analyses of cohort studies have found an inverse association between moderate coffee consumption and risk of CAD [182], or no association between coffee and CAD [183-185]. On the other hand, meta-analyses of case-control studies have reported a higher risk of CAD for coffee consumers [183, 184]. A recent meta-analysis showed that moderate coffee consumption also was inversely associated with risk of stroke [186].

Little is known about the impact of coffee consumption on risk of VTE. Only one observational study has investigated the association between coffee consumption and the risk of VTE [187]. The Iowa Women's Health Study (IWHS) is a prospective cohort study of nearly 40 000 women aged 55-69 at time of study inclusion [187]. A total of 1 950 events of VTE evolved during a median follow-up of 13 years. They reported that coffee was inversely associated with risk of VTE in analyses adjusted for age, caloric intake, educational level, smoking status and physical activity (p for trend 0.04). However, the association was attenuated after adjustments for diabetes and BMI (28-<42 servings/week, hazard ratio (HR): 0.88 , 95% CI: 0.74-1.05, ≥42 servings/week, HR: 0.86, 95% CI: 0.69-1.06)(p for trend 0.11) [187].

1.6 Psychosocial factors and the risk of venous thromboembolism

Hemingway and Marmot define a psychosocial factor *as a measurement that potentially relates psychological phenomena to the social environment and to pathophysiological changes* [188]. Some of these factors may be clinical depression and depressive symptoms, loneliness and social support, chronic stress, optimism and positive affect. Positive affect reflects the level of pleasurable engagement of an individual with the environment, and covers terms like enthusiasm, joy, happiness, excitement and contentment [189].

Psychosocial factors have been related to health outcomes, especially to arterial cardiovascular disease. Positive affect and optimism have been related to beneficial effects on all-cause mortality [190] and cardiovascular mortality [191]. An inverse association between incident CAD and optimism or positive affect has also been reported in cohort studies [192, 193]. Conversely, negative factors such as stress, depression, depressive symptoms, loneliness and lack of social support, have been associated with higher mortality [194-198]. The risk of incident MI has been associated with stress, both at home and at work, financial stress, and stressful life events [199, 200]. Depression and depressive symptoms have also been predictive of incident CAD [201, 202]. In addition, higher risk of CAD has been reported among chronically lonely women [203] and among female homemakers feeling lonely [204]. Knowledge about the association between VTE and psychosocial factors is limited. Only one observational study has aimed to prospectively investigate the relation between psychosocial factors, in terms of persistent stress, and risk of VTE among 6 958 middle-aged men [205]. They found that persistent stress was related to higher risk of pulmonary embolism (HR: 1.66, 95% CI: 1.12-2.48), but was not associated with the risk of DVT in multivariable analyses (HR: 1.21, 95% CI: 0.78-1.89) [205]. To our

knowledge, other psychosocial factors, such as depression and depressive symptoms, loneliness and social support, optimism and positive affect have not been investigated with regard to VTE in observational studies.

1.7 Smoking and the risk of venous thromboembolism

Tobacco use is a major cause of morbidity and mortality, and is the leading cause of preventable death. It is estimated that cigarettes kill more than 5 million people yearly worldwide [206]. Its association with increased risk of cardiovascular disease is well established [207, 208], but the findings concerning smoking and risk of VTE remain conflicting. Several studies have failed to find an association between smoking and risk of VTE [24, 73, 78, 162, 209, 210], while other observational studies have found an increased risk among current and former smokers [211], among current smokers only [212, 213] and some have found increased risk of VTE among heavy smokers only [80, 214-216]. Suggested mechanisms for this potential association are smoking-induced increased levels of coagulation factors [217] and fibrinogen [218, 219], impaired fibrinolysis [220], endothelial dysfunction [221] and increased platelet aggregation [222, 223].

The Physicians' Health study, a cohort study of 18 662 male physicians followed for a median of 20.1 years, studied the association between smoking and CAD and VTE in the same population, and found that current and former smokers had increased risk of CAD, but not increased risk of VTE [24]. Similar findings were reported in the Longitudinal Investigation of Thromboembolism Etiology (LITE) study, a prospective cohort study of men and women aged ≥45 years, in which no association between smoking status or number of pack-years and risk of VTE was found [78]. However, recent results from the LITE study demonstrated

that smoking status was a risk factor for VTE in time-dependent analyses in which exposure variables including smoking status were updated during follow-up [212]. Smoking status was not associated with risk of VTE in the Tromsø study [73] and in the "Helseundersøkelsen I Nord-Trøndelag" (HUNT) study [162]. A meta-analysis including 21 studies supports these findings of no association, but only four prospective studies were included in these analyses [209].

On the other hand, a large case-control study (MEGA) of 3 989 cases and 4 900 controls found an increased risk of VTE among current and former smokers [211]. Furthermore, daily amounts of cigarettes were associated with increased risk of VTE in a dose-dependent manner [211]. A Danish prospective study (DCH) of 57 053 middle-aged men and women, found that current smokers had increased risk of VTE [213]. In addition, the authors suggested a threshold effect since women smoking more than 20 cigarettes, and men smoking more than 30 cigarettes, had a markedly higher risk of VTE compared to those who smoked less [213]. Heavy smoking has also been associated with VTE in several other cohort studies [80, 214-216]. Results from the Copenhagen City Heart Study (CCHS) showed that smoking ≥25 g tobacco daily was associated with higher risk compared to the risk of never smokers [216]. Similar findings were found in The Nurses' Health Study in which smoking at least 25 cigarettes/day yielded an elevated risk of pulmonary embolism among middle-aged nurses [80]. Smoking more than 100 000 cigarettes ever was positively associated with VTE risk in the Swedish Melanoma Inquiry of Southern Sweden (MISS) study of women only [215], and smoking ≥15 g tobacco daily was a risk factor for VTE in another Swedish cohort of middle-aged men [214]. Furthermore, the Iowa Women's Health Study (IWHS), a cohort of elderly women only, reported a 20% higher risk of VTE among current and former smokers

(HR: 1.18, 95% CI: 1.06-1.31 and HR: 1.19, 95% CI: 1.04-1.36, respectively), as well as a higher risk among heavy smokers (≥20 pack-years) compared to never smokers [224]. However, the association was restricted to provoked VTE only, and this association was attributed to cancer-associated VTE [224]. Even though there are some evidence about VTE and smoking, there are few studies that are based on a general population, and that have information about other smoking-attributable diseases, such as MI and cancer, during follow-up.

1.8 Socioeconomic status and the risk of venous thromboembolism

Socioeconomic status (SES) has been defined as the social position of an individual compared to other members of the same society [225]. The three most commonly used indicators of SES are educational level, occupational status and income, but other measures such as housing tenure, household overcrowding and material goods, can also be used as SES indicators [225]. Socioeconomic status has impact on health outcomes and life expectancy. SES has especially been associated with incident cardiovascular disease [226-228], cardiovascular mortality [229, 230] and overall mortality [230-232] in Western countries. Modifiable and behavioural risk factors can at least partially explain differences in the incidence of arterial CVD across social classes [227]. Other factors that may explain the observed association are psychosocial factors, parental risk factors, work-related risk factors, residence and neighbourhood conditions, inequalities in health services including both treatments and accessibility to health care [225].

The results of the existing observational studies about the association between SES and VTE risk point to an inverse or no association. A Swedish cohort study of 6 958 men which investigated the relation between SES and risk of VTE, found that men with high

occupational status had lower risk of PE compared to men with lower occupational status (HR: 0.57, 95% CI: 0.39-0.83), whereas no association was found between occupational class and risk of DVT [205]. The relation between educational status and household income and risk of VTE was investigated in a Danish cohort (CCHS) of 18 954 men and women. Household income was found to be inversely associated with VTE risk, but the investigators failed to find any association between educational level and risk of VTE in multivariable analyses [216]. Results from the IWHS showed that women with education higher than high school level had lower risk of VTE compared to women without high school education (HR:0.87, 95% CI: 0.77-0.97) [224]. An inverse association between education and risk of VTE was also found among Swedish women in the MISS-study (education of <9 years vs. ≥12 years, HR: 1.6, 95% CI: 1.2-2.2) [215]. Furthermore, two recent registry-based studies have reported inverse associations between educational level, certain occupations, income and risk of VTE [233, 234]. On the other hand, the prospective LITE study and a case-control study of women did not find any association between educational level and risk of VTE [78, 235]. The diverging study results may be explained by different SES indicators as most studies have only investigated one or two indicators of SES. Furthermore, most of them have refrained from taking potential behavioural factors, psychosocial factors or other potential explanatory factors into account.

2. AIMS OF THE THESIS

Even though there are many recognised risk factors for VTE, 25-50% of all VTE events are unprovoked, i.e. without an identifiable risk factor present at time of diagnosis [25]. Discovery of novel risk factors for VTE may contribute to strategies for prevention and further understanding of the pathophysiology of VTE. Living a healthy lifestyle is emphasized in the primary and secondary prevention of arterial CVD such as myocardial infarction. The impact of specific lifestyle factors on the risk of VTE is not well known. Extended knowledge on the association between lifestyle factors, such as coffee consumption, emotional states, smoking and socioeconomic status, and risk of VTE may provide recommendations of behaviour to protect against VTE.

The aims of this thesis were:

- To investigate the association between coffee consumption and risk of incident VTE in a prospective, population-based study.
- To investigate the impact of emotional states on the risk of VTE.
- To examine the association between smoking and risk of VTE where other smoking-attributable diseases are taken into account.
- To investigate the association between socioeconomic status and risk of VTE, and to investigate the impact of behavioural factors, psychosocial factors and comorbidity on this relation.

3. STUDY POPULATION AND METHODS

3.1 The Tromsø study

The Tromsø study is a single-centre, population-based study with repeated surveys of the inhabitants of the municipality of Tromsø, Norway. The Department of Community Medicine at the University of Tromsø is responsible for the management of the study. The study was carried out for the first time in order to investigate reasons for the high cardiovascular mortality in northern Norway. In all, six studies have been conducted, the first in 1974 and the following in 1979-80, 1986-87, 1994-95, 2000-01, and 2007-08. All four papers of this thesis are based on data from the fourth Tromsø study, which was conducted in 1994-95. All inhabitants aged 25 years or older living in the municipality of Tromsø were invited to participate, and a total of 27 158 subjects participated (participation rate of 77%). In paper I, II and III, the subjects were followed from the date of enrolment in the Tromsø study until September 1, 2007 and all incident events of VTE occurring during this time-period were identified. The follow-up time was extended to December 31, 2010 in paper IV.

3.2 Baseline measurements

Baseline data was collected by self-administered questionnaires, blood samples and a physical examination by trained personnel. Information about lifestyle factors including coffee consumption, cigarette smoking, emotional states and indicators of socioeconomic status was collected by self-reports through questionnaires (presented in the appendix). To assess coffee consumption, participants were asked to report the daily consumption of cups of boiled coffee and of other types of coffee. The total number of cups was combined into one single variable for total coffee consumption, which was categorized into 0 cups (coffee abstainers), 1-2 cups, 3-4 cups, 5-6 cups or more than 6 cups daily. Smoking habits were

assessed by questions on smoking status, number of cigarettes smoked daily and number of years as smokers. This information was used to make variables for smoking status and smoking dose in pack-years (1 pack-year equals 20 cigarettes daily for one year). Participants were asked about their emotions during the last 2 weeks, did they feel happy and optimistic, depressed, or lonely. There were four response alternatives, which were modified into 3-level variables due to low numbers of participants in the upper categories. Furthermore, participants were asked about their educational level (7-10 years of school, 10-12 years, 13-15 years (high school diploma), <4 years at college/university, ≥4 years at college/university), their self-perceived health (poor, not so good, good, very good) and satisfaction with number of friends (yes/no). Employment status was based on information about paid work, homemakers, unemployment, education or military service, social benefits and old age pension and number of weekly hours of paid work. Data about confounders, such as oestrogen use, diabetes, dietary habits, alcohol consumption and physical activity were collected by the self-administered questionnaire. Non-fasting blood samples were collected from the antecubital vein. Serum was prepared by centrifugation after one hour respite at room temperature and further analysed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were measured by enzymatic, colorimetric methods and commercially available kits (CHOD-PAP for cholesterol, GPO-PAP for triglycerides, Boeringer Mannheim). Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Blood pressure was recorded by use of an automatic device (Dinamap Vital Signs Monitor) of specially trained personnel. Participants rested for 2 minutes in a sitting position, followed by 3 measurements on the right upper arm, separated by 2-minute intervals. The mean of the two last readings was used in the analyses. Participants were

dressed in light clothing and no shoes when height and weight were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Personal net income was obtained from Statistics Norway. Cancer diagnoses prior to baseline were obtained from the Cancer registry of Norway.

3.3 Outcome measurements

3.3.1 Venous thromboembolism

All incident events of VTE during follow-up were identified by searching the hospital discharge diagnosis registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway. The university hospital is the only hospital in the region, and all outpatient consultations and hospitalizations are provided by this single hospital. The relevant codes were *International Classification of Disease* version 9 (ICD-9) codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9 for the time period 1994-98, and ICD-10 codes I26, I80, I81, I82, I67.6, O22.3, O22.5, 087.1, O87.3 for the period 1999-2010. The hospital discharge diagnosis registry included diagnoses from outpatient clinic visits and hospitalizations. The radiology procedure registry was used to find potential cases of objectively confirmed VTE that were missed due to coding errors in the hospital discharge diagnosis registry. All relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during follow-up, were systematically reviewed by trained personnel, and cases of objectively confirmed VTE were found. An additional search through the computerized index of autopsy diagnoses was conducted and additional events of VTE were identified.

To validate the VTE events, the medical record for each potential VTE patient was reviewed by trained personnel. The personnel 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 fulfilled; (1) objectively confirmed by diagnostic procedures as 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 agent), thrombolytics or vascular surgery unless contraindications were specified in the medical record. VTE events deriving from the autopsy registry were recorded as an outcome when the death certificate indicated VTE as cause of death or as a significant condition contributing to death.

The VTE events were further classified as provoked or unprovoked, depending on the presence of risk factors at the time of diagnosis. The 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 travel exceeding 4 hours within the last 14 days prior to the event). If none of these were present, the event was classified as unprovoked.

3.3.2 Myocardial infarction and cancer

Events of myocardial infarction were identified and validated in the CVD registry of the Tromsø study. The events were found by searching through the hospital discharge diagnosis registry at the University Hospital of North Norway, where they were identified by ICD-9 codes 410-414 in the time period 1994-98, and ICD-10 codes I20-25 and I60-69 in the time period thereafter. Validation of the MI events was conducted by trained personnel reviewing the medical records of each potential MI patient. Slightly modified WHO MONICA/MORGAM criteria were used, and included signs and symptoms, findings in electrocardiogram, elevated cardiac biomarkers and autopsy reports where applicable. Fatal cases of incident MI that were not admitted to hospital were identified by linkage to the National Causes of Death Registry at Statistics Norway. Information from death certificates was used to collect relevant information from reports and records from nursing homes, general practitioners and ambulance services.

Data on cancer diagnoses were obtained by linkage to the Cancer Registry of Norway in which the date of the cancer diagnosis and other cancer characteristics were registered. The registry is considered as a valid registry where the completeness has been estimated at 98.8% for the time-period 2001-2005, where 93.8% of the cases were morphologically verified [236].

4. MAIN RESULTS

4.1 Paper I: COFFEE CONSUMPTION AND THE RISK OF VENOUS THROMBOEMBOLISM: THE TROMSØ STUDY

Coffee consumption has been associated with several health outcomes. The results of studies investigating the relation between arterial CVD and coffee are diverging, where both an inverse association and a detrimental effect of coffee consumption have been suggested. To our knowledge, only one observational study among elderly women only has investigated the association between coffee and VTE risk, in which they failed to find any association. The aim of this prospective population-based study was to investigate the association between coffee consumption and risk of VTE. Baseline information, including coffee consumption given as number of cups of coffee consumed on a daily basis, was obtained in 26 755 subjects aged 25-97 years who participated in the fourth Tromsø study in 1994-95. Intake of coffee was categorized into 5 categories: 0 cups daily, 1-2 cups daily, 3-4 cups daily, 5-6 cups daily and more than 6 cups daily. Incident VTE events were identified and validated from enrolment date until September 1, 2007. There were 462 VTE events during a median of 12.5 years of follow-up. Subjects drinking 3-4 cups of coffee daily had a HR of 0.70 (95% CI: 0.48-1.02) for risk of VTE compared to coffee abstainers in multivariable analyses adjusted for age, sex, BMI, smoking, physical activity, diabetes, cancer and cardiovascular disease. Drinking 5-6 cups was associated with more than 30% lower risk of VTE compared to coffee abstainers (HR 0.67, 95% CI: 0.45-0.97). Drinking less or more coffee was not significantly associated with risk of VTE. Additional adjustments for caloric intake did not influence the observed association. We concluded that moderate coffee consumption was inversely associated with risk of VTE, suggesting a U-shaped relation between coffee intake and the risk of VTE.

4.2 Paper II: EMOTIONAL STATES AND FUTURE RISK OF VENOUS THROMBOEMBOLISM. THE TROMSØ STUDY

The relation between psychosocial factors and risk of arterial CVD has been given much attention, whereas knowledge about psychosocial factors and risk of VTE is limited. Results from a cohort study of middle-aged men showed that self-perceived stress was associated with risk of PE. The association between emotional states and risk of VTE has previously not been explored. The aim of our study was to investigate the association between emotional states such as feelings of depression, loneliness, happiness and optimism and the risk of incident VTE in a prospective, population-based study. A total of 25 964 subjects aged 25-96 years participating in the fourth Tromsø study in 1994-95 were included. Feelings of depression, loneliness, happiness and optimism during the last 2 weeks before study participation were reported by self-administered questionnaires, along with other potential confounders and comorbidities. Incident VTE events were registered from date of study inclusion to September 1, 2007. A total of 440 VTE events were identified and validated during follow-up (median 12.7 years). Those who often felt depressed had 1.6-fold higher risk of VTE compared to those who did not feel depressed (HR: 1.59, 95% CI: 1.01-2.49). Feelings of happiness and optimism were inversely associated with risk of VTE (frequent feelings of happiness/optimism vs. not happy/optimistic, HR: 0.60, 95% CI: 0.41-0.88). Feelings of loneliness were not associated with VTE risk, but those who felt concurrently depressed and lonely had a higher incidence rate than those who felt depressed only (age and sex adjusted IR: 3.27 vs. 2.21). Feelings of depression were especially associated with unprovoked VTE, while feelings of happiness and optimism were inversely associated with both provoked and unprovoked VTE. Our findings suggested that emotional states were associated with the risk of VTE.

4.3 Paper III: CIGARETTE SMOKING AND RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

There is a substantial amount of evidence regarding the association between smoking and the risk of VTE, but the conclusions remain conflicting. Assessment of cigarette smoking has varied in the different studies. Some have investigated smoking status only, whereas others also have explored smoking dose and duration. This study aimed to explore the association between cigarette smoking and VTE. Smoking status (current, never, former) as well as smoking dose, duration and number of pack-years were assessed. Information on smoking habits and other baseline variables were obtained in 24 576 adults aged 25-96 years participating in the fourth Tromsø study (1994-95). Incident events of VTE were reported from study enrolment until September 1, 2007. There were 389 events of VTE during the follow-up of a median of 12.5 years. Current and former smokers had HRs of 1.21 (95% CI: 0.93-1.56) and 1.13 (95% CI: 0.88-1.45), respectively, compared to never-smokers. Heavy smokers (>20 pack-years) had higher risk of total VTE (HR: 1.46, 95% CI: 1.04-2.05) and provoked VTE (HR: 1.75, 95% CI: 1.14-2.69) in multivariable analyses adjusted for age, sex, BMI and higher education. Cause-specific analyses revealed that cigarette smoking was associated with increased risk of myocardial infarction and cancer, but was not associated with risk of VTE (HR: 1.04, 95% CI: 0.67-1.61). In conclusion, heavy smoking was associated with provoked VTE. Our findings suggested that this association was mediated through other smoking-attributable diseases.

4.4 Paper IV: SOCIOECONOMIC STATUS AND RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

Mortality and morbidity, particularly due to cardiovascular disease, differ across levels of socioeconomic status. However, whether these differences also hold true for VTE is less clear. To date, studies conclude that there is no association or an inverse association between socioeconomic status and VTE. The objective of this study was to investigate the association between socioeconomic status and risk of VTE, and to evaluate the impact of behavioural factors, psychosocial factors and comorbidity on this association. Baseline information was collected in 26 473 men and women aged 25-97 years. A modified version of the Socioeconomic Condition Index (SCI) was used as SES indicator, and was based on the following variables: educational level, employment status, personal net income, self-perceived health and satisfaction with number of good friends. Participants were followed from baseline until December 31, 2010. A total of 602 VTE events were identified during follow-up (median 15.8 years). An inverse association between SCI score and risk of VTE was found among women only. Women in the highest quartile of SCI (SCI 15-18 points) had lower risk of VTE compared to women in the lowest quartile (SCI 0-8 points) in age-adjusted analyses (HR: 0.44, 95% CI: 0.27-0.72), and in multivariable analyses (HR: 0.62, 95% CI: 0.36-1.05) (p for trend across quartiles of SCI: 0.02). Among the individual components, educational level and self-perceived health were the strongest predictors of risk of VTE. Behavioural factors explained 30-40% of the association. No association was found between SCI or its individual components and risk of VTE among men. Our study suggested that SCI was inversely associated with risk of VTE among women only. Behavioural factors explained 30-40% of the observed association between SCI and risk of VTE in women.

5. GENERAL DISCUSSION

5.1 Methodological considerations

5.1.1 Causality

Epidemiologic studies intend to study cause and effect relations. However, to find an association between exposure and outcome does not imply causality. Guidelines for establishing causality were defined by Bradford Hill, although they were not originally intended to be used as a checklist. The guidelines include the following considerations [237]: *Strength of association, biological gradient, consistency, specificity, temporality, plausibility, coherence, experiment* and *analogy*. *Strength of association* implies that a strong association is more likely to have a causal component than a modest association. The presence of a *biological gradient* means observation of a dose-response relationship between exposure and outcome. Both strength of the association and a dose-response relationship can be measured in cohort studies, in terms of absolute and relative risk estimates. *Consistency* means that the association is repeatedly observed in different studies using different study design and populations. *Specificity* implies that one exposure influences one particular outcome. It is difficult to meet this criterion as VTE is a multicausal disease which implies that several risk factors must be present in order for VTE to develop. Similarly, lifestyle factors also have impact on many health conditions. *Temporality* implies that the exposure must precede the outcome of interest*,* which is fulfilled by a prospective cohort as exposure is obtained before the outcome. *Plausibility* means that the observed association can be plausibly explained by biological mechanisms or other explanations. C*oherence* means that the results fit into the existing theory. E*xperiment* implies that the findings are based on randomized experiments. A cohort study fails to meet this criterion due to its observational design. *Analogy* can be explained as an effect that already has been shown for similar

exposures and outcomes. As randomized controlled trials (RCT) are experimental, it is considered the gold-standard for establishing causality. Other epidemiologic studies can investigate associations, but cannot establish causality.

5.1.2 Study design

All four papers of this thesis are based on data from a population-based, prospective cohort study. A cohort study follows participants from study enrolment until they develop the outcome of interest, or until end of the study. The aim of a cohort study is to compare the incidence of an outcome in exposed subjects to the incidence of non-exposed subjects, yielding both absolute and relative risk estimates, in terms of incidence rates and relative risks [238]. Case-control studies include individuals with an outcome of interest, and match these subjects with controls without the outcome. Subsequently, information about exposure is collected in the same manner among cases and controls. These studies are usually retrospective as information about exposure is collected from the past in terms of self-reports or data from databases. Proportions of exposure among cases and controls are compared, and yields relative risk estimates as odds ratios [238]. Case-controls studies are favourable in case of rare outcomes and are cost-effective as information about outcome and exposure can be collected simultaneously. Both cohort studies and case-control studies can be subject to confounding and selection bias. In contrast to case-control studies, a prospective cohort study collects the exposure variables prior to, and independently of the outcome. The prospective design has the clear temporal sequence between exposure and outcome, which is considered in the question of causality. Additionally, it eliminates the chance of recall bias that may occur in retrospective case-control studies in which information about exposure may be influenced by the outcome. Case-control studies are

also subject to reverse causation, as blood samples often are collected after the VTE event has occurred. Thus, results can be influenced by the VTE event, which can be illustrated by studies of high sensitive C-reactive protein (hs-CRP), an inflammatory marker, and the association with VTE. A case-control study found an association between hs-CRP and unprovoked VTE [239], whereas no association was reported in a cohort study [240] and in a prospective study of CRP genotypes [241]. These findings may reflect that inflammation is a reaction of the VTE event, and not the other way around.

Randomized controlled trials are comparable to cohort studies since they have the same aim and overall design. However, the major difference between these designs is the fact that cohort studies are observational, while randomized trials are experimental, as the exposure is assigned to the participants by the study investigators. In addition, allocation of subjects in exposure categories is random in RCTs. In cohort studies, exposure is not inflicted, and allocation of study subjects in exposure categories is therefore not random. This can lead to unequal distribution of variables which may affect both the exposure and outcome, i.e. confounding. Bias due to confounding should not occur in RCTs if the allocation is random. Although RCTs are considered the gold-standard, the study design also has its disadvantages. The external validity may be limited in RCTs due to strict inclusion and exclusion criteria. In addition, RCTs are expensive and time-consuming, and certain RCTs cannot be carried out due to ethical reasons. To investigate the association between smoking and VTE by the implementation of a RCT would be difficult due to ethical considerations. In addition, the price and time consumption of such a study would not justify the results, as the study would have to carry on for many years to identify enough outcomes. With these types of research

questions, observational studies are a good alternative, although they have obvious limitations in order to determine a causal relationship.

Mendelian randomization has been developed to establish causality within observational studies utilizing the concept of random assignment of alleles in gamete formation during conception, which can mimic the randomization of a clinical trial [242]. The allele variants of interest are associated with modifiable risk factors, and are therefore used as proxy measures of these risk factors to study the association with health outcomes [242]. The risk of confounding is minimized as random assignment of alleles makes the differences in participants' characteristics due to chance, except for the difference which is a result of the genetic variant [243]. In addition, reverse causation is also avoided as the genotype is fixed at conception and not influenced by underlying disease [244]. There are certain assumptions underlying Mendelian randomization. The genetic variant must be reliably associated with the factor of interest, and the association between the disease and the genetic variant must be mediated through the factor of interest [242]. In addition, the genetic variant must be independent of other confounders [242]. Knowledge about the function of the genetic variant and its neighbouring variants is needed to evaluate whether the assumptions are fulfilled. Genetic heterogeneity (a phenotype are caused by several alleles), pleiotropy (one allele cause many phenotypes) and canalization (the process where the same phenotype is developed regardless of genetic variation due to buffering of compensatory developmental processes) are examples of factors that complicate the use of Mendelian randomization [244]. Another issue is population stratification in which the frequency of genetic variants, exposures or outcomes varies significantly between subgroups of the study population. This problem can be solved by having homogeneous study populations [243]. The Mendelian

randomization approach has been applied in order to study the causal association between HDL cholesterol and myocardial infarction [245]. Many observational studies have shown that high levels of HDL are associated with reduced risk of MI [246, 247]. In contrast, this study found by Mendelian randomization that a genetic score based on certain SNPs, which was associated with HDL level, was not associated with risk of myocardial infarction [245]. These findings have challenged the concept of a protective effect of high HDL on risk of MI. In the future, Mendelian randomization can be a useful tool to study the concept of causality for many of the factors recognized as risk factors for VTE today.

5.1.3 External validity

External validity is the applicability of the results to a defined population [248]. In order to obtain high external validity, the study population must be representative of the reference population. Representativeness rely on eligibility criteria for study inclusion, a high participation rate and stability of the cohort during follow-up (low number of subjects lost to follow-up) [248]. The Tromsø study is a population-based study defined by the geographical boundaries of the municipality of Tromsø. All adults inhabitants aged 25 or older were invited to participate in the fourth study, and 77% of the eligible population participated. Tromsø is a city of 69 000 inhabitants (2011) [249] and is situated about 400 kilometres north of the Arctic Circle [250] where nearly all of the inhabitants of Tromsø are Caucasians. The living standard of the Tromsø population is relatively high, and comparable to other Western countries in terms of age and sex-distribution, educational level and lifestyle factors. The VTE incidence found in our population is comparable to the incidence found in other Western countries [21-23]. Based on the abovementioned facts, we argue that the external validity of our study is high for Western populations. However, the participation

rate were lower among those younger than 30 years and those older than 80 years. Thus, the external validity may be lower in these age groups. In addition, there was a higher proportion of men among the non-attendees compared to the attendees, and they were more likely to be single than attendees [250]. Furthermore, a lower attendance among disabled and those with severe illness is likely to have occurred and may have led to selection bias.

5.1.4 Confounding and effect modification (interaction)

As already mentioned, cohort studies are non-experimental and exposure classification is not randomly assigned. This may lead to unequal distribution of other characteristics leading to bias and confounding. A confounder is defined as a variable associated with both the exposure and the outcome, and it is not an intermediate on the pathway between the exposure and outcome [251]. Confounding may lead to under- or overestimation of the true association or it may even turn the direction of the association. The association between coffee consumption and risk of VTE presented in paper I were potentially subject to confounding by cigarette consumption as cigarette smoking was unequally distributed across coffee categories, and as cigarette smoking may be associated with the risk of VTE.

There are several strategies for reducing confounding [238] in observational cohort studies. Restriction of study participants to for example women only can reduce confounding, but will also reduce the external validity. In the phase of data analysis, measures of potential confounders can be included as covariates in multivariable regression models or the data can be stratified by these confounders [238]. However, these strategies do not reduce potential bias related to unmeasured or unknown confounders [252]. Hence, statistical control for potential confounders does not replace the need of randomized trial in which

randomization to treatment group minimizes the risk of confounding, including confounding by unidentified confounders (residual confounding).

Of the strategies mentioned, multiple regression models are most commonly used, and allow us to examine the unique contribution of each independent exposure variable in a model [253]. Multivariable proportional hazard analyses have been presented in all four papers in order to consider the effect of lifestyle factors when other exposure variables are taken into account. However, residual confounding cannot be ruled out. Potential sources of residual confounding are improper definitions of potential confounders, lack of information about potential confounders and unknown confounders. For instance, when including smoking status (current smoker yes/no, or current/never/former smoker) as a potential confounder, there may still be residual confounding as the risk of VTE may be dependent on the amount of smoking and not the smoking status per se [80, 214-216]. In paper IV, an inverse association between SES and risk of VTE in women was found, and only 30-40% of this association was explained by behavioural factors. Inclusion of feelings of happiness did not affect the risk estimates, but other psychosocial factors such as stress, personality traits or job strain are factors that potentially could have influenced the results. Unfortunately, the Tromsø study lack information about such variables, and confounding by these factors cannot be ruled out. Furthermore, information on hereditary thrombophilia was not available. However, only 3% of the VTE events were related to hereditary thrombophilia measured at the time of VTE diagnosis. To our knowledge, there are no association between hereditary thrombophilia and lifestyle, thus, we do not believe that hereditary thrombophilia represent a strong confounder in our study.

In paper 4, all analyses were presented in sex-specific analyses. This was due to interaction between sex and one of the components of the Socioeconomic Condition Index. Effect modification, or statistical interaction, is defined as the effect of one exposure on an outcome is changed by the value of a second exposure [253]. Sex-specific analyses were therefore performed, showing the risk estimates for SCI and its components separately for men and women.

5.1.5 Misclassification and information bias

Collection of data may be imprecise and erroneous due to unfit collection methods and inaccurate questions. This may lead to misclassification, which results in information bias, and can threat the internal validity of the study. Internal validity is defined as the validity of the results for the study population, and is dependent on the quality of the methods [251]. Misclassification can be *differential*, meaning that the exposure is misclassified differently for those with or without the outcome, or the outcome is misclassified differently for the exposed and the non-exposed, or *non-differential,* information on exposure or outcome is misclassified unrelated to outcome or exposure, respectively [254]. Non-differential misclassification usually leads to dilution of the effect, while differential misclassification can exaggerate or underestimate the effect [254]. This can lead to both type I and type II errors. A type I error (measured by *p*) is to reject the null hypothesis when it is no real association present, whereas a type II error is to accept the null hypothesis when there actually is an association present [255].

Recall bias in retrospective case-control studies is an example of differential misclassification as responding to questions about exposure from the past may depend on an individual's case-control status [254]. Cases may give more accurate information about exposure than

controls. To obtain information from the past can also be a source of non-differential misclassification since remembering previous exposure can be difficult for everyone, independent of case-control status. In a prospective study, exposure is measured prior to outcome, hence, the exposure misclassification is generally non-differential. In the Tromsø study, information about VTE events was collected by personnel blinded to exposure status, supporting the misclassification of events is likely non-differential.

Due to a large number of study participants and limited funding, use of self-administered questionnaires is common in cohort studies, such as the Tromsø study. All data on lifestyle was self-reported through questionnaires, and is a potential source of misclassification. Assessing coffee consumption by self-administered questionnaires has been shown to have high validity when comparing with diet records. Questionnaires on self-reported smoking have also been shown to have high validity [256, 257]. Assessing smoking status by self-reported questionnaires seems preferable to interviewer-administered questionnaires as responders tend to respond more socially desirable in interviewer-based questionnaires [258]. However, others have shown that self-reports of smoking is an underestimation of the prevalence of smoking measured by serum cotinine levels [259], so we cannot exclude the possibility of misclassification. Regarding psychosocial factors as emotional states, most existing studies have used clinical definitions or standardized questionnaires or interviews [191-193, 201], rather than single-item questions. The questions used in the second paper have not been validated, and it cannot be ruled out that the questions may have covered concepts of personality traits or other factors, rather than emotional states. However, using single-item questions have been predictive of certain outcomes in previous reports [203, 204], and the face validity of the single-item questions may be an advantage. Self-reported

diabetes is one of the potential confounders included in multivariable models. The prevalence of diabetes among adults (≥20 years) is reported to be nearly 6% in developed countries in 1995 [260], while less than 2% of our study population stated to have diabetes in the self-reported questionnaire of 1994/95. Thus, underreporting of diabetes is probably present and may have led to misclassification.

5.1.6 Modifiable risk factors

The Tromsø study has a long follow-up period of more than 12 years in all four papers, while the exposure variables of interest in this thesis were collected at baseline in 1994-1995 only. Lifestyle factors are examples of modifiable factors that may change over time. It is likely that exposures and risk profiles of the study participants have changed during follow-up, leading to regression dilution bias, an underestimation of the real association [261], which may introduce type II error. This was demonstrated in the Framingham study where associations between outcome and baseline variables were underestimated by 1/3 after one decade 1/2 after two decades [261]. The non-significant association between smoking status and VTE may have been a result of regression dilution due to change of smoking habits, especially smoking cessation. About 1/3 of the Norwegian population were daily smokers in 1995-1999, but only 25% smoked daily in 2003-2007 [262]. As a counter-argument, cause-specific analyses for smoking and risk of VTE, MI and cancer were conducted, and showed that smoking was strongly associated with risk of cancer and MI, but was not associated with VTE risk. Using a proportional hazard model with time-dependent exposure variables can reduce the risk of regression dilution. Such analyses have been reported from the LITE study in which analyses using regular Cox regression models showed no association between VTE

and smoking status [78], whereas models using Cox regression with time-dependent exposure variables revealed that smoking status was a risk factor for VTE [212].

5.1.7 Outcome measurements: registration and validation

In the Tromsø study, events of VTE were registered from study enrolment until September 1, 2007 in paper I-III, and until December 31, 2010 in paper IV as the follow-up of VTE events was extended. The events were identified by searching the hospital discharge diagnosis registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway where both hospitalizations and outpatient clinic consultations were included. The University Hospital of North Norway is the single specialist health care provider in the region, which enhances the chance of a complete VTE registry. However, we cannot exclude that some VTE events were diagnosed and treated somewhere else, and were therefore missed. Validation of the VTE events was performed by evaluating medical records of each potential VTE patient to avoid false positive events. A VTE event had to fulfil all four criteria listed in the section of methods: symptoms and signs were present, the diagnoses were objectively confirmed, a physician had made the diagnosis of DVT/PE and treatment was demanded. Patients who had asymptomatic thrombi discovered by CT, and were not treated with anticoagulants or surgery, were not considered clinical VTE events. Using these validation criteria has enabled us to study clinically relevant VTE events, while registration of asymptomatic events has been avoided.

Despite the use of validation criteria, risk of misclassification of outcome cannot be excluded. A retrospective collection of outcome measurement is dependent on accurate and complete information from medical records to obtain valid outcomes. There was no

standard procedure for registration of the circumstances of the event in the medical records. The categorization of provoked and unprovoked events of VTE relied on the information provided for each patient. Personnel who validated the VTE events were blinded to baseline characteristics, thus we believe that the feasible misclassification is non-differential, leading to underestimation of the real effect. Unfortunately, we did not have information about previous VTE events prior to baseline among the healthy study participants who did not experience VTE during follow-up. Prevalent cases of VTE prior to baseline should have been excluded from the analyses instead of contributing with person-years to the population at risk. However, this concerns only a small fraction of the participants, and would probably have insignificant effects on the risk estimates.

5.1.8 Missing values

Missing data are quite common in epidemiologic studies, which can be due to respondent refusal to answer, skipped questions, technical errors during procedures or loss to follow-up [263]. Careful planning and execution of the study are paramount to reduce the introduction of missing values [264]. Deletion and imputation are techniques for dealing with missing data when present. The whole variable should be omitted if it contains a large percentage of missing values [265]. Other techniques involving deletion are listwise and pairwise deletion. Listwise deletion is elimination of all data concerning one subject with missing data in certain variables, whereas pairwise deletion only excludes data on subjects in statistical analyses where the missing information is needed [264]. These methods lead to reduction of statistical power and are subjects to potential bias since the techniques assume that the data are missing completely at random. Bias and reduction of power can be avoided using

imputation techniques. These approaches involve replacing the missing values with estimates based on other variables of the data set.

For all papers of this thesis, a combination of listwise and pairwise deletion has been performed to deal with missing data. Subjects with missing values for the exposure of interest have been deleted, while missing values in covariates have been omitted in the relevant analyses. In paper IV, 3689 subjects (14%) missed information about "satisfaction with number of good friends". These subjects differed from the non-missing subjects in terms of age, sex, educational level and income. In order to avoid bias and loose power, multiple imputation was performed. We assumed that these values were missing at random (MAR), meaning that the missing values of a variable depend on observed data and are independent of the variable itself [266]. Twenty imputed datasets were created based on the other SCI variables, plus age, sex, the outcome variable VTE, and the Nelson-Aalen estimate of the baseline cumulative hazard, and used in the Cox regression analyses.

5.2 Discussion of main results

Behavioural factors are clustered. Cigarette smoking is associated with alcohol consumption, an unhealthy diet is associated with an unfavourable weight [267]. Paper IV shows the distribution of typical atherosclerotic risk factors and behavioural factors across the socioeconomic gradient. Those with low socioeconomic status have higher prevalence of atherosclerotic risk factors and unhealthy behavioural factors. Among those with low SES, there are a higher proportion of current smokers, they have a higher BMI, and they are less physically active than those with higher SES. Thus, to evaluate the influence of one behavioural factor on the risk of a health outcome is difficult. Similarly, it is also challenging

to differentiate between risk factors that are causally related to VTE, and those that are merely markers for causal factors (innocent bystanders). Such hypotheses are impossible to test in clinical trials, due to both economy and ethical considerations. Mendelian randomization studies could, however, be useful in identifying the causal factors among many risk factors.

Coffee consumption

Coffee consists of many components, and its effects on health have been attributed to ingredients as caffeine, diterpenes, chlorogenic acid and other antioxidants [176]. Caffeine has been associated with stimulation of the nervous system, acute elevation of blood pressure, increased diuresis and metabolic rate [268]. The University of Tromsø is recognised for the finding of the association between coffee intake and increased cholesterol levels [269], which was later ascribed to the diterpenes in boiled coffee [270]. Polyphenols, as chlorogenic acid, have antioxidant properties which may affect the oxidation of LDL cholesterol, as well as influence platelet aggregation [271, 272] and possibly endothelial dysfunction [273, 274]. Few studies have investigated the effects of coffee on other haemostatic variables as coagulation factors [275] and fibrinolysis [276-279], and the results are diverging.

To our knowledge, few epidemiologic studies have investigated the association between coffee consumption and risk of VTE. Our findings from the Tromsø study suggested that drinking 3-6 cups of coffee daily was inversely associated with risk of VTE. The Iowa Women's Health Study also found a lower risk of VTE among coffee drinkers, but this association was attenuated after multivariable adjustments [187]. The lack of significant

findings may have been due to lack of power as the risk estimates pointed towards an inverse association [187]. In addition, it can be difficult to reveal a modest association in an elderly study population as these subjects have higher background risk. Regression dilution is another potential explanation for their findings as the IWHS started accruing person-years at 65 years of age, which resulted in a gap between time of baseline measurements and time at risk for some of the study participants [187]. Recent results from the MEGA study, a case-control study of 1 803 cases and 1 803 partner controls confirmed our findings by finding a 25% lower risk among coffee consumers compared to coffee abstainers (HR: 0.75, 95% CI: 0.55-1.04) [280]. In addition, they found that the inverse association was mediated through the haemostatic factors factor VIII and VWF, which are associated with increased risk of VTE. The authors speculated about the underlying mechanisms and suggested that polyphenols may be involved in the pathogenesis of their findings [280]. As polyphenols may have effects on platelet aggregation and endothelial dysfunction, polyphenols may influence levels of haemostatic factors, such as VWF, since VWF is synthesized and stored in endothelial cells, megakaryocytes and platelets [281].

Since only observational studies have investigated whether coffee may have impact on the risk of VTE, residual confounding cannot be excluded. As observed in our study, as well as in other studies [282], coffee consumption was associated with lower socioeconomic status and unfavourable behavioural factors such as cigarette smoking, alcohol use, less physical exercise and unhealthy dietary habits compared to coffee abstainers. Adjustments for age, sex, BMI, smoking status and daily caloric intake were added to the model without attenuating our results. Similar actions were done in the IWHS where risk estimates were attenuated when behavioural factors as smoking, education, caloric intake, physical activity

and BMI were included in the model [187]. The MEGA study used partners of cases as controls because couples tend to have similar behaviour as well as socioeconomic status [280]. Hence, this matching took unmeasured factors into account. In addition, they adjusted for BMI, smoking status, alcohol use and hormonal factors in the multivariable analyses [280]. In all three studies, the risk estimates pointed towards an inverse association after multivariable adjustments. Not all of the risk estimates were statistically significant, but this may have been due to lack of power. Another explanation for the observed association between coffee consumption and risk of VTE is comorbidity. Individuals diagnosed with chronic or serious disease may stop drinking coffee as coffee consumption has been perceived as part of an unhealthy lifestyle. In that sense, coffee consumption would not be inversely associated with risk of VTE, but it would rather be a marker of good health, which would most likely lower the risk of VTE. In our cohort, coffee abstainers did not have a higher prevalence of arterial CVD, cancer or diabetes than coffee consumers. As expected, inclusion of these factors in the multivariable analysis did not influence the results. In the MEGA study, adjustments for even more chronic diseases and medications did not affect the size of the risk estimates. Furthermore, the decreased risk among coffee drinkers was also found for unprovoked VTE both in our study and in the MEGA study [280]. These arguments undermine the hypothesis of underlying disease being the reason for our findings.

A problem with the cohort design that applies to both the Tromsø study and the IWHS, is the measurement of exposure variables at one point in time only. Coffee consumption is a modifiable behavioural factor which may change over time. This results in non-differential misclassification leading to attenuation of the results (regression dilution bias), suggesting that the real association between coffee and VTE risk might be stronger than what we have

observed. Thus, it is expected that measuring coffee consumption at several points in time would strengthen the risk estimates. The MEGA-study, a case-control study, does not have the problem of regression dilution, but may be subject to differential misclassification and recall bias which could lead to under- or overestimation of the real association.

The similar findings in two cohort studies and one case-control study reduce the likelihood that our findings are due to chance. However, additional observational studies should assess whether this observed association is present in other study populations, to ensure firm conclusions on the association between coffee consumption and VTE. Furthermore, a randomized controlled trial could be appropriate as observational studies cannot establish causality. However, investigating the effect of coffee consumption on endpoints such as VTE would be time-consuming and resource-demanding. Alternatively, further efforts could be invested in potential mechanistic studies for the relation between coffee consumption and VTE risk.

Emotional states

The relationship between different emotional states and the risk of VTE has not been investigated previously. Of other psychosocial factors, only self-perceived stress has been found to increase the risk of PE [205]. We found that frequent feelings of depression were associated with a nearly 60% higher risk of VTE, whereas those feeling often happy and optimistic had 40% lower risk of VTE. Our findings on VTE are in agreement with previous findings about psychosocial factors and arterial CVD [192, 193, 201, 202]. The largest case-control studies who have investigated the association between antidepressants and risk of VTE, have only found that current use of amitriptyline (tricyclic antidepressant) was

associated with increased risk of VTE [283], whereas there was no association between use of other antidepressants and risk of VTE [283, 284]. This can suggest that amitriptyline itself, rather than the depressive condition, is associated with VTE. Unfortunately, information about use of antidepressants was not available in our study.

There are several plausible explanations for our findings. First, health behavioural factors are likely to be connected with emotional states. It has been shown that depressed subjects are more likely smokers [285], they drink more alcohol and are less physically active [286, 287], as observed among those feeling frequently depressed in our study as well. Second, material factors may also confound the observed association as psychosocial factors are related to social status [288]. We adjusted for behavioural factors as well as socioeconomic status by educational level and disability pension. However, the association can still be attributed to residual confounding. Third, feelings of depression/happiness and optimism may also be markers for underlying health problems as emotions are related to state of health, and VTE events often are results of other diseases, hospitalizations, treatments and immobilization. However, adjustments for CVD, cancer, self-reported diabetes and disability pension did not affect our risk estimates. In addition, the strongest associations were between feelings of depression or happiness/optimism and risk of unprovoked VTE, suggesting that the association was not due to underlying disease.

Fourth, direct physiological pathways may also play a part. Alterations of the autonomous nerve system and the hypothalamic-pituitary-adrenal axis, platelet function, the immune system, and the haemostatic system have been associated with psychosocial factors [289]. Acute mental stress has been associated with increased levels of coagulation parameters as

of FVII, FVIII:C, FXII:C and VWF [290, 291], increased fibrinolysis in terms of increased t-PA activity and t-PA antigen [291], and platelet activation and aggregation [292, 293]. Activation of the coagulation and fibrinolytic system has been observed in anxiety patients experiencing acute fear of blood drawing [294], which may trigger the same mechanisms as acute stress reactions. Low social support has also been associated with higher D-dimer and fibrinogen before and after acute stress [295]. Studies investigating the relation between depression and platelet function are conflicting, as some reported increased platelet activation among depressed patients, while the majority of studies found no association between depression and platelet activation and responsiveness [296]. Both positive and negative findings were reported from studies that have investigated the association between clinical depression and depressive symptoms and markers of coagulation and fibrinolysis [296-302]. An association between depressive mood and coagulation factors VII and X has been reported [300]. However, other reports have suggested that depression and pessimism may be related to an inflammatory state rather than disturbances of the haemostatic system [301, 302]. Anxiety and depression among VTE patients have been associated with higher levels of protein S and protein C [303]. Furthermore, depression and low social support have been associated with enhanced coagulation activity (higher levels of d-dimer and shortened activated partial thromboplastin time (aPTT)) in VTE patients [304].

Cigarette smoking

The studies investigating the association between smoking and risk of VTE have diverging results. There are several possible explanations for the different findings. First, comorbidity may have impact on the risk estimates as nearly 10% of smokers have smoking-attributable diseases [207]. We found an increased risk of VTE among heavy smokers (smoking>20 pack-

years, HR: 1.46, 95% CI: 1.04-2.05). However, no association between smoking and risk of VTE was found when events of myocardial infarction and cancer were taken into consideration in cause-specific hazard analyses (> 20 pack-years, HR: 1.04, 95% CI: 0.67-1.61). The Physicians' Health Study reached similar conclusions as smoking was associated with risk of CAD and stroke, but not with risk of VTE, in cause-specific analyses of VTE, CAD and stroke [24]. Furthermore, the IWHS found that current and former smokers were at increased risk of provoked VTE only, and that this association was driven by cancer-related provoked VTE [224]. In contrast, smoking remained associated with VTE risk among men after adjustments for cancer, MI, stroke and diabetes mellitus during follow-up in "The Study of Men Born in 1913" [214]. Most of the studies that found an association between smoking and VTE, have excluded cases of cancer or/and MI prior to baseline [80, 213, 215], but did not take comorbidity during follow-up into consideration [80, 213, 215, 216].

Second, smoking doses may explain the diverging results. Most studies which have investigated smoking doses in addition to smoking status, have found increased risk of VTE among heavy smokers [80, 214-216]. Results from the DCH study showed that doses exceeding 20 g tobacco/day for women and 30 g tobacco/day for men were associated with a higher risk of VTE than lower smoking doses, suggesting a threshold effect [213]. Most studies that explored smoking status only, concluded that smoking is not a risk factor for VTE [73, 162, 210]. On the other hand, the DCH Study [213] and the MEGA study [211] found an association between smoking status and VTE, as well as an association between smoking doses and VTE risk. The diverging effect of smoking status may be attributed to different distribution of light and heavy smokers. A high proportion of light smokers among current smokers in the Tromsø study, as well as in other studies, may explain the lack of association

between current smoking and risk of VTE. However, there are also studies that did not find an increased risk of VTE among heavy smokers [78]. These studies did not adjust for BMI which may be an important confounder as smoking is associated with lower BMI [305].

Third, study design could be of importance. As cohort studies have measured smoking a long time prior to the outcome, it cannot be excluded that cohort studies, including the Tromsø study, are subjects to misclassification and thereby fail to find an association due to regression dilution. The LITE study found no association between smoking status and risk of VTE in Cox regression analyses (current smoking, HR: 1.03, 95% CI: 0.71-1.49) [78], but recent results from the LITE study revealed an association between smoking status and risk of VTE using time-dependent analyses in which exposure variables, including smoking status, were updated during follow-up (current smoking, HR: 1.44, 95% CI: 1.12-1.86) [212]. Case-control studies are not subject to regression dilution, but can be affected by recall bias as smokers and non-smokers could report their cigarette consumption differently.

Socioeconomic status

Results from the Tromsø study showed an inverse association between SES and risk of VTE among women, whereas no association was found among men. A sex-specific difference in the association between SES and VTE has not been reported previously, but the number of studies about SES and VTE is limited. There are several cohort studies among women that reported an inverse association between educational level and risk of VTE [215, 224]. On the other hand, a relation between SES and VTE risk has also been reported among men, as high occupational class was associated with decreased risk of PE in a Swedish cohort [205]. The association between education and risk of VTE was stronger among women than men in age-

and calendar time-adjusted analyses in the CCHS, but only household income, and not educational level, was associated with risk of VTE after multivariable adjustments in pooled analyses of men and women [216]. Furthermore, two registry-based studies among men and women also found associations between education, income and certain occupations and risk of VTE, but the analyses were not adjusted for important confounders such as BMI [233, 234]. An interaction between sex and SES has also been reported in studies of SES and risk of arterial CVD, in which the difference in incidence and mortality of arterial CVD was greater across the socioeconomic gradient in women than in men [227, 228, 306, 307].

Behavioural factors, psychosocial factors and comorbidity have been proposed to explain the relation between SES and health outcomes [225]. We found that behavioural factors explained 30-40% of the association between indicators of SES and risk of VTE, in contrast to studies about SES and risk of arterial CVD where behavioural factors accounted for about 50% of the association [226, 227]. This could imply that modifiable behavioural factors have greater impact on arterial CVD compared to the development of VTE. However, it is likely that residual confounding exists. It is likely to assume that other behavioural factors could be of importance for the association. Diet was not included in our analyses, but previous results from Tromsø failed to identify any association between a heart healthy diet and risk of VTE [308]. In addition, updated information on behavioural factors during follow-up could enlarge the impact of these factors on the relation between SES and VTE, as demonstrated for total mortality [309]. Inclusion of psychosocial factors and comorbidity in the statistical models did not affect the risk estimates. However, only feelings of happiness and optimism were included. Information about other psychosocial factors, such as stress, job strain and personality traits could potentially have influenced the results.

To measure SES, we used the Socioeconomic Condition Index, which is a modified version of the Living Condition Index (LCI) [310]. The LCI is based on a set of variables used to describe the needs of an acceptable life in a European society [311] where all components of the index are equally weighed. Unfortunately, none of these indexes have been validated. In addition, using an index as SES indicator has been discussed previously and was not recommended due to problems arising from the individual components, as well as the weighing of the components when constructing the index [312]. Arguments in favour of using an index are that it could embrace broader aspects of SES rather than one indicator alone. Furthermore, SES indicators can be influenced by cultural and demographic factors. Thus, the meaning of SES indicators can vary between societies, age groups and sexes, which can make the use of an index more representative. In addition, certain SES indicators can be affected by comorbidity (e.g. income) while others remain constant (e.g. education). Self-perceived health and educational level were the strongest predictors of VTE in our female population. Self-perceived health is not a traditional marker for SES, but several studies have shown that it is a predictor of CAD [313] and overall mortality [314]. Education is the most commonly used indicator of SES as it has been more strongly associated with outcomes of disease and cardiovascular risk factors compared to other SES indicators [315]. It has usually low non-response rates and is easily answered [312]. Moreover, it is usually fixed, and not affected by health in adult age [312]. On the other hand, education can be affected by childhood health, and there are different educational norms in different societies and in different age cohorts [315]. This was also observed in our study, as the mean age of those with low educational level was higher than the age of those with high education. However, there was no statistical interaction between age and the SCI-indicators. The other indicators

of SES can change, while educational level is usually stable over time. The less apparent inverse association between the other indicators and risk of VTE, may be due to regression dilution bias caused by non-differential misclassification of these variables.

6. CONCLUSIONS

We found that coffee consumption was inversely associated with risk of VTE. A moderate coffee consumption was associated with about 30% lower risk of VTE compared to coffee abstinence. Our findings were recently confirmed in a large case-control study.

Subjects who reported frequent feelings of depression during the last two weeks before study start had nearly 60% higher risk of VTE compared to those who reported no such feelings. Contrary, frequent feelings of happiness and optimism were associated with a 40% lowered risk of VTE. Future confirmative studies should be conducted using standardized questionnaires with updates during follow-up.

Heavy smoking, defined as >20 pack-years, was apparently associated with increased risk of VTE, and the increased risk was restricted to provoked VTE. The significant association disappeared in cause-specific analyses when smoking-related diseases, such as MI and cancer, were taken into consideration. Our findings suggest that smoking-attributable diseases or other predisposing factors are essential for smoking to convey a risk of VTE.

We found socioeconomic status to be inversely associated with risk of VTE among women, but not among men. Educational level and self-perceived health were the strongest predictors of VTE risk. About 30-40% of the association between SCI and its components and risk of VTE was explained by behavioural factors, whereas the emotional state and comorbidity did not affect the risk estimates. Residual confounding due to other behavioural and psychosocial factors cannot be ruled out.

Certain lifestyle factors seem to be associated with risk of VTE even though the number of studies is limited. The findings of this thesis point in the same direction as reports from many other studies about other health outcomes, especially arterial CVD. These findings can be an important contribution to the perception of a healthy lifestyle in a public health perspective. Even though the risk estimates are not so high, the prevalence of lifestyle factors in the population makes lifestyle factors important modulators of incident VTE in the population.

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Paper I

Paper II

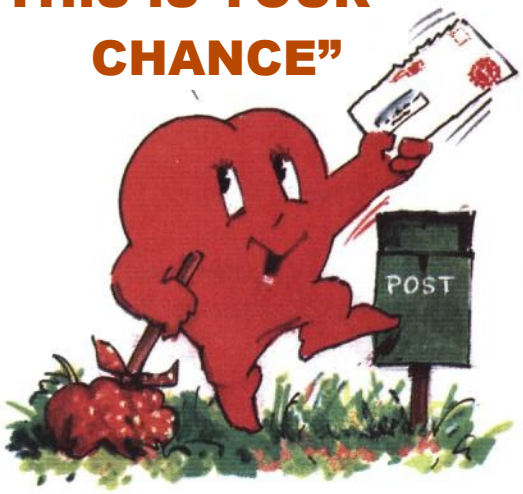
Paper III

Paper IV

Appendix

HEALTH SURVEY
Invitation

"THIS IS YOUR CHANCE"



Date of birth **Social security No.** **Municipality** **Electoral ward No.**

Welcome to the Tromsø Health Survey!

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

"THIS IS A REAL OPPORTUNITY- TAKE IT!"

YOUR OWN HEALTH

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

Poor	12	1
Not so good		2
Good		3
Very good		4

Do you have, or have you had:

		Yes	No	Age first time
A heart attack	13			years
Angina pectoris (heart cramp)	16			years
A cerebral stroke/ brain haemorrhage	19			years
Asthma	22			years
Diabetes	25			years

Do you use blood pressure lowering drugs?

Currently	28	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? 29 Yes / No

Have you in the last two weeks felt:

		No	A little	A lot	Very much
Nervous or worried?	30				
Anxious?	31				
Confident and calm?	32				
Irritable?	33				
Happy and optimistic?	34				
Down/depressed?	35				
Lonely?	36				
		1	2	3	4

SMOKING

Did any of the adults at home smoke while you were growing up? 37 Yes / No

Do you currently, or did you previously, live together with daily smokers after your 20th birthday? 38 Yes / No

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

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

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

Do you yourself smoke:

		Yes	No
Cigarettes daily?	43		
Cigars/ cigarillos daily?	44		
A pipe daily?	45		

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

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you usually smoke per day? 48 ____ cigarettes

How old were you when you began daily smoking? 52 ____ Age years

How many years in all have you smoked daily? 54 ____ Years

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.

		Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)*	56				
Hard activity *(sweating/ out of breath)*	57				
		1	2	3	4

COFFEE

How many cups of coffee do you drink daily?

Put 0 if you do not drink coffee daily.

Coarsely ground coffee for brewing 58 ____ Cups

Other coffee 60 ____ Cups

ALCOHOL

Are you a teetotaller? 62 Yes / No

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 ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? 65

Do not count low-alcohol beer.

Put 0 if less than once a month.

Beer	Wine	Spirits
Glasses	Glasses	Glasses

FAT

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

Don't use butter/margarine	71	1
Butter		2
Hard margarine		3
Soft margarine		4
Butter/margarine mixtures		5
Light margarine		6

EDUCATION/WORK

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school	72	1
Technical school, middle school, vocational school, 1-2 years senior high school		2
High school diploma (3-4 years)		3
College/university, less than 4 years		4
College/university, 4 or more years		5

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 ____ No. of hours

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

Yes	No	Don't know

Tromsø Health Survey
for the over 70s

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

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 ❑

Day Month Year

Date for filling in this form: .....18 ...../...../.....

CHILDHOOD/YOUTH

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

.....24 -28

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

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

- Very good .....29 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

How old were your parents when they died?

- Mother .....30 _____Years
- Father .....32 _____Years

HOME

Who do you live with?
Tick once for each item and give the number.

	Yes	No	Number
Spouse/partner 34	❑	❑	
Other people over 18 years 35	❑	❑	_____
People under 18 years 38	❑	❑	_____

What type of house do you live in?

- Villa/ detached house .....41 ❑ 1
- Farm ..... ❑ 2
- Flat/apartment ..... ❑ 3
- Terraced /semi-detached house ..... ❑ 4
- Other ..... ❑ 5

How long have you lived in your present home? .....42 _____years

	Yes	No
Is your home adapted to your needs? 44	❑	❑
If "No", do you have problems with:		
Living space 45	❑	❑
Variable temperature, too cold/too warm 46	❑	❑
Stairs 47	❑	❑
Toilet 48	❑	❑
Bath/shower 49	❑	❑
Maintenance 50	❑	❑
Other (please specify) 51	❑	❑

Would you like to move into a retirement home? ...52 ❑ ❑

PREVIOUS WORK AND FINANCIAL SITUATION

How will you describe the type of work you had for the last 5-10 years before you retired?

- Mostly sedentary work? .....53 ❑ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ❑ 2
  (e.g. shop assistant, housewife, teaching)
- Work that requires a lot of walking and lifting? ..... ❑ 3
  (e.g. postman, nurse, construction)
- Heavy manual work ..... ❑ 4
  (e.g. forestry, heavy farm-work, heavy construction)

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

	Yes	No
Driver 54	❑	❑
Farmer 55	❑	❑
Fisherman 56	❑	❑

How old were you when you retired? .....57 _____Years

What kind of pension do you have?

- Basic state pension .....59 ❑
- An additional pension .....60 ❑

How is your current financial situation?

- Very good .....61 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse .....62 ❑ 1
- No, unchanged ..... ❑ 2
- Yes, it has got better ..... ❑ 3

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

- Much worse .....63 ❑ 1
- A little worse ..... ❑ 2
- About the same ..... ❑ 3
- A little better ..... ❑ 4
- Much better ..... ❑ 5

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	Yes	No	Age
Hip fracture 64	❑	❑	_____
Wrist /forearm fracture 67	❑	❑	_____
Whiplash 70	❑	❑	_____
Injury requiring hospital admission 73	❑	❑	_____
Gastric ulcer 76	❑	❑	_____
Duodenal ulcer 79	❑	❑	_____
Gastric/duodenal ulcer surgery 82	❑	❑	_____
Neck surgery 85	❑	❑	_____

Have you ever had, or do you have:
Tick one box only for each item.

	Yes	No
Cancer 88	❑	❑
Epilepsy	❑	❑
Migraine	❑	❑
Parkinson's disease	❑	❑
Chronic bronchitis	❑	❑
Psoriasis 93	❑	❑
Osteoporosis	❑	❑
Fibromyalgia/fibrositis/chronic pain syndrome	❑	❑
Psychological problems for which you have sought help	❑	❑
Thyroid disease	❑	❑
Liver disease 98	❑	❑
Recurrent urinary incontinence	❑	❑
Glaucoma	❑	❑
Cataract	❑	❑
Arthrosis (osteoarthritis)	❑	❑
Rheumatoid arthritis 103	❑	❑
Kidney stones	❑	❑
Appendectomy	❑	❑
Allergy and hypersensitivity		
Atopic eczema (e.g. childhood eczema)	❑	❑
Hand eczema	❑	❑
Hey fever 108	❑	❑
Food allergy	❑	❑
Other hypersensitivity (not allergy)	❑	❑

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

	Yes	No
Have you had this in the last 14 days? 113	❑	❑

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.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 114	❑	❑	❑	❑	❑	❑
Heart attack before age 60 120	❑	❑	❑	❑	❑	❑
Cancer 126	❑	❑	❑	❑	❑	❑
Hypertension 132	❑	❑	❑	❑	❑	❑
Asthma 138	❑	❑	❑	❑	❑	❑
Osteoporosis 144	❑	❑	❑	❑	❑	❑
Arthrosis (osteoarthritis) 150	❑	❑	❑	❑	❑	❑
Psychological problems 156	❑	❑	❑	❑	❑	❑
Dementia 162	❑	❑	❑	❑	❑	❑
Diabetes 168	❑	❑	❑	❑	❑	❑
- age when they got diabetes 174	__	__	__	__	__	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? 184	❑	❑
If "Yes":		
Is your cough productive? 185	❑	❑
Have you had this kind of cough for as long as 3 months in each of the last two years? 186	❑	❑
Have you had episodes with wheezing in your chest?187	❑	❑
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 188	❑	❑
In connection with respiratory infections	❑	❑
In connection with physical exertion	❑	❑
In connection with very cold weather 191	❑	❑
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 192	❑	❑
Have you lost weight in the last year? 193	❑	❑
If "Yes":		
How many kilograms? 194	_____ kg	

How often do you suffer from sleeplessness?

- Never, or just a few times a year .....196 ❑ 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 .....197 ❑ 1
- Especially during the polar night ..... ❑ 2
- Especially during the midnight sun season ..... ❑ 3
- Especially in spring and autumn ..... ❑ 4

	Yes	No
Do you usually take a nap during the day? 198	❑	❑
Do you feel that you usually get enough sleep?	❑	❑

Do you suffer from:	No	A little	A lot
Dizziness 200	❑	❑	❑
Poor memory	❑	❑	❑
Lack of energy	❑	❑	❑
Constipation 203	❑	❑	❑

Does the thought of getting a serious illness ever worry you?

- Not at all ..... 204 ☐
- Only a little ..... ☐
- Some ..... ☐
- Very much ..... ☐

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?	Yes	With some help	No
Walking indoors on one level 205	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself 210	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating	☐	☐	☐
Cooking 215	☐	☐	☐
Doing light housework *(e.g. washing up)*	☐	☐	☐
Doing heavier housework *(e.g. cleaning floor)* ..	☐	☐	☐
Go shopping	☐	☐	☐
Take the bus	☐	☐	☐

	Yes	With difficulty	No
Can you hear normal speech (if necessary with hearing aid)? 220	☐	☐	☐
Can you read (if necessary with glasses)? 221	☐	☐	☐

Are you dependent on any of the following aids? ?

	Yes	No
Walking stick 222	☐	☐
Crutches	☐	☐
Walking frame/zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device..... 227	☐	☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to vour own health or illness:
Put 0 if you have not had such contact

	Number of times the past year
To a general practitioner (GP)/emergency GP 228	
To a psychologist or psychiatrist	
To an other medical specialist (not at a hospital)	
To a hospital out-patient clinic 234	
Admitted to a hospital	
To a physiotherapist	
To a chiropractor 240	
To a acupuncturist	
To a dentist	
To a chiropodist 246	
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	
To a healer, faith healer, clairvoyant	

Do you have home aid?	Yes	No
Private 252	☐	☐
Municipal	☐	☐

Do you receive home nursing care? ..... ☐ ☐

Are you pleased with the health care and home assistance services in the municipality?

	Yes	No	Don't know
Assigned family GP 255	☐	☐	☐
Home nursing care	☐	☐	☐
Home assistance services	☐	☐	☐

Do you feel confident that you will receive health care and home assistance services if you need it?

- Confident ..... 258 ☐ 1
- Not confident ..... ☐ 2
- Very unsure ..... ☐ 3
- Don't know ..... ☐ 4

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the last 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:

- Painkillers ..... 259 _____months
- Sleeping pills ..... _____months
- Tranquillizers ..... _____months
- Antidepressants ..... 265 _____months
- Allergy drugs ..... _____months
- Asthma drugs ..... _____months
- Heart medicines (not blood pressure) ..... 271 _____months
- Insulin ..... _____months
- Diabetes tablets ..... _____months
- Drugs for hypothyroidism (Thyroxine) ..... 277 _____months
- Cortisone tablets ..... _____months
- Remedies for constipation ..... _____months

Dietary supplements:

- Iron tablets ..... 283 _____months
- Vitamin D supplements ..... _____months
- Other vitamin supplements ..... _____months
- Calcium tablets or bone meal ..... 289 _____months
- Cod liver oil or fish oil capsules ..... _____months

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? 293	Yes	No
	☐	☐
If "Yes", who can give you help?		
Spouse/partner 294	☐	
Children	☐	
Others	☐	

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

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

	Yes	No
Do you feel you have enough good friends?..... 299	☐	☐

Do you feel that you belong to a community (group of people) who can depend on each other and who feel committed to each other (e.g. a political party, religious group, relatives, neighbours, work place, or organisation)?

- Strong sense of belonging ..... 300 ☐ 1
- Some sense of belonging ..... ☐ 2
- Not sure ..... ☐ 3
- Little or no sense of belonging ..... ☐ 4

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 ..... 301 ☐ 1
- 1-2 times a month ..... ☐ 2
- Approximately once a week ..... ☐ 3
- More than once a week ..... ☐ 4

FOOD HABITS

Number

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?

Tick one or two boxes.

	White Bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread type is most similar to:	☐ 306	☐	☐	☐	☐ 310

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

- Butter ..... 311 ☐
- Hard margarine ..... ☐
- Soft margarine ..... ☐
- Butter/margarine blend ..... ☐
- Oils ..... 315 ☐

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

Tick one box for each foodstuff.

	None	Less than 1	1-2	3 or more
Milk of all types (glasses) 316	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐
Slices of bread with				
– fish (e.g. mackerel in tomato sauce)	☐	☐	☐	☐
– cheese *(e.g. Gouda/Norvegia)*	☐	☐	☐	☐
– smoked cod caviare 322	☐ 1	☐ 2	☐ 3	☐ 4

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

Tick for all foodstuffs listed.

	Never	Less than 1	1	2 or more
Yoghurt 323	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐
Breakfast cereal/oatmeal, etc.	☐	☐	☐	☐
Dinner with				
– unprocessed meat	☐	☐	☐	☐
– fatty fish (e.g. salmon/red-fish)	☐	☐	☐	☐
– lean fish (e.g. cod) 328	☐	☐	☐	☐
– vegetables (fresh or cooked)	☐	☐	☐	☐
Carrots (fresh or cooked)	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐
Oranges, mandarins, etc. 333	☐ 1	☐ 2	☐ 3	☐ 4

WELL BEING

How content do you generally feel with growing old?

- Good ..... 334 ☐ 1
- Quite good ..... ☐ 2
- Up and down ..... ☐ 3
- Bad ..... ☐ 4

What is your view of the future?

- Bright ..... 335 ☐ 1
- Not too bad ..... ☐ 2
- Quite worried ..... ☐ 3
- Dark ..... ☐ 4

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 336 _____ years

How old were you when you stopped menstruating? ..... 338 _____ years

PREGNANCY

How many children have you given birth to? ..... 340 _____ Children

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birth year and number of months you breastfed at the space provided below for comments.

Child	Year of birth:	Number of months breastfed:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 366 Yes ☐ No ☐

If "Yes", during which pregnancy?	Pregnancy First	Later
High blood pressure 367	☐	☐
Proteinuria 369	☐	☐

ESTROGEN

Do you use, or have you ever used estrogen:

	Now	Previously	Never
Tablets or patches 371	☐	☐	☐
Cream or suppositories 372	☐	☐	☐

If you use estrogen, what brand do you currently use?

..... 373

Your comments:

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

Tromsø Health Survey

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 ☐

Day Month Year

Date for filling in this form:..... 18 ...../...../.....

CHILDHOOD/YOUTH

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

..... 24 - 28

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

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

- Very good ..... 29 ☐
- Good ..... ☐
- Difficult ..... ☐
- Very difficult ..... ☐

How many of the first three years of your life

- did you live in a town/city? ..... 30 ____years
- did your family have a cat or dog in the home? ..... 31 ____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

HOME

Who do you live with?

Tick once for each item and give the number .		Yes	No	Number
Spouse/partner	36	☐	☐	
Other people over 18 years	37	☐	☐	_____
People under 18 years	40	☐	☐	_____

How many of the children attend day care/kindergarten? .... 43 _____

What type of house do you live in?

- Villa/detached house ..... 45 ☐ 1
- Farm ..... ☐ 2
- Flat /apartment ..... ☐ 3
- Terraced /semi-detached house ..... ☐ 4
- Other ..... ☐ 5

How big is your house? ..... 46 _____ m^2

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

		Yes	No
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?

- Electric heating ..... 56 ☐
- Wood-burning stove ..... ☐
- Central heating system using:
  - Paraffin ..... ☐
  - Electricity ..... ☐

		Yes	No
Do you have fitted carpets in the living room?	60	☐	☐
Is there a cat in your home?	61	☐	☐
Is there a dog in your home?	62	☐	☐

WORK

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

- Mostly sedentary work? ..... 63 ☐ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ☐ 2
  (e.g. shop assistant, light industrial work, teaching)
- Work that requires a lot of walking and lifting? ..... ☐ 3
  (e.g. postman, nursing, construction)
- Heavy manual work? ..... ☐ 4
  (e.g. forestry, heavy farm-work, heavy construction)

Can you decide yourself how your work should be organised?

- No, not at all ..... 64 ☐ 1
- To a small extent ..... ☐ 2
- Yes, to a large extent ..... ☐ 3
- Yes, I decide myself ..... ☐ 4

		Yes	No
Are you on call, do you work shifts or nights?	65	☐	☐

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

Tick one box only for each item.		Yes	No
Driver	66	☐	☐
Farmer		☐	☐
Fisherman		☐	☐

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time.
*If you have had the condition several times, how old were you **last** time?*

	Yes	No	Age
Hip fracture 69	❑	❑	_____
Wrist/forearm fracture 72	❑	❑	_____
Whiplash 75	❑	❑	_____
Injury requiring hospital admission 78	❑	❑	_____
Gastric ulcer 81	❑	❑	_____
Duodenal ulcer 84	❑	❑	_____
Gastric/duodenal ulcer surgery 87	❑	❑	_____
Neck surgery 90	❑	❑	_____

Have you you ever had, or do you still have:
Tick one box only for each item.

	Yes	No
Cancer 93	❑	❑
Epilepsy	❑	❑
Migraine	❑	❑
Chronic bronchitis	❑	❑
Psoriasis	❑	❑
Osteoporosis 98	❑	❑
Fibromyalgia/fibrositis/chronic pain syndrome	❑	❑
Psychological problems for which you have sought help	❑	❑
Thyroid disease	❑	❑
Liver disease	❑	❑
Kidney disease 103	❑	❑
Appendectomy	❑	❑
Allergy and hypersensitivity:		
Atopic eczema (e.g. childhood eczema)	❑	❑
Hand eczema	❑	❑
Hay fever	❑	❑
Food allergy 108	❑	❑
Other hypersensitivity (not allergy)	❑	❑

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

	Yes	No
Have you had this in the last 14 days? 112	❑	❑

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.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 113	❑	❑	❑	❑	❑	❑
Heart attack before age 60 119	❑	❑	❑	❑	❑	❑
Cancer 125	❑	❑	❑	❑	❑	❑
Asthma 131	❑	❑	❑	❑	❑	❑
Gastric/duodenal ulcer 137	❑	❑	❑	❑	❑	❑
Osteoporosis 143	❑	❑	❑	❑	❑	❑
Psychological problems 149	❑	❑	❑	❑	❑	❑
Allergy 155	❑	❑	❑	❑	❑	❑
Diabetes 161	❑	❑	❑	❑	❑	❑
– age when they got diabetes 167	___	___	___	___	___	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? ..177	❑	❑
If "Yes":		
Is your cough productive ? 178	❑	❑
Have you had this kind of cough for as long as 3 months in each of the last two years? 179	❑	❑
Have you had episodes of wheezing in your chest? ..180	❑	❑
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 181	❑	❑
In connection with respiratory infections	❑	❑
In connection with physical exertion	❑	❑
In connection with very cold weather	❑	❑
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 185	❑	❑

How often do you suffer from sleeplessness?

Never, or just a few times a year 186	❑ 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 187	❑ 1
Especially during the polar night	❑ 2
Especially during the midnight sun season	❑ 3
Especially in spring and autumn	❑ 4

	Yes	No
Have you in the last year suffered from sleeplessness to the extent that it has affected your ability to work? ..188	❑	❑

How often do you suffer from headaches?

Rarely or never 189	❑ 1
Once or more a month	❑ 2
Once or more a week	❑ 3
Daily	❑ 4

Does the thought of getting a serious illness ever worry you?

Not at all 190	❑ 1
Only a little	❑ 2
Some	❑ 3
Very much	❑ 4

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:
*Tick **0** if you have **not** had such contact*

	Number of times the past year
To a general practitioner (GP)/Emergency GP 191	_____
To a psychologist or psychiatrist	_____
To an other medical specialist (not at a hospital)	_____
To a hospital out-patient clinic 197	_____
Admitted to a hospital	_____
To a medical officer at work	_____
To a physiotherapist 203	_____
To a chiropractor	_____
To an acupuncturist	_____
To a dentist 209	_____
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	_____
To a healer, faith healer, clairvoyant	_____

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

Painkillers	215	_____ months
Sleeping pills		_____ months
Tranquillizers		_____ months
Antidepressants	221	_____ months
Allergy drugs		_____ months
Asthma drugs		_____ months

Dietary supplements

Iron tablets	227	_____ months
Calcium tablets or bonemeal		_____ months
Vitamin D supplements		_____ months
Other vitamin supplements	233	_____ months
Cod liver oil or fish oil capsules		_____ months

Have you in the last 14 days used the following medicines or dietary supplements?
*Tick **one** box only for **each** item.*

		Yes	No
Medicines			
Painkillers	237	❑	❑
Antipyretic drugs (to reduce fever)		❑	❑
Migraine drugs		❑	❑
Eczema cream/ointment		❑	❑
Heart medicines (not blood pressure)		❑	❑
Cholesterol lowering drugs		❑	❑
Sleeping pills		❑	❑
Tranquillizers		❑	❑
Antidepressants		❑	❑
Other drugs for nervous conditions		❑	❑
Antacids	247	❑	❑
Gastric ulcer drugs		❑	❑
Insulin		❑	❑
Diabetes tablets		❑	❑
Drugs for hypothyroidism (Thyroxine)		❑	❑
Cortisone tablets	252	❑	❑
Other medicine(s)		❑	❑
Dietary supplements			
Iron tablets		❑	❑
Calcium tablets or bonemeal		❑	❑
Vitamin D supplements		❑	❑
Other vitamin supplements	257	❑	❑
Cod liver oil or fish oil capsules		❑	❑

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 _____ good 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? ..... 261 _____

	Yes	No
Do you feel you have enough good friends? 263	❑	❑

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	264	❑ 1
1-2 times a month		❑ 2
Approximately once a week		❑ 3
More than once a week		❑ 4

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 ..... 265 _____ slices

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

Butter	266	❑
Hard margarine		❑
Soft margarine		❑
Butter/margarine blend		❑
Oils	270	❑

What kind of bread (bought or home-made) do you usually eat?
Tick one or two boxes!

	White bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread I eat is most similar to:	❑ 271	❑	❑	❑	❑ 275

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.*

	0	Less than 1	1-2	3-4	5-6	More than 6
Full milk (ordinary or curdled) (glasses) 276	❑	❑	❑	❑	❑	❑
Semi-skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Tea (cups)	❑	❑	❑	❑	❑	❑
Orange juice (glasses)	❑	❑	❑	❑	❑	❑
Potatoes 281	❑	❑	❑	❑	❑	❑
Slices of bread in total (incl. crisp-bread)	❑	❑	❑	❑	❑	❑
Slices of bread with						
- fish (e.g. mackerel in tomato sauce)	❑	❑	❑	❑	❑	❑
- lean meat (e.g. ham)	❑	❑	❑	❑	❑	❑
- fat meat (e.g. salami)	❑	❑	❑	❑	❑	❑
- cheese *(e.g. Gouda/ Norvegia)* 286	❑	❑	❑	❑	❑	❑
- brown cheese	❑	❑	❑	❑	❑	❑
- smoked cod caviare	❑	❑	❑	❑	❑	❑
- jam and other sweet spreads	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

How many **times per week** do you normally eat the following foodstuffs?
*Tick a box for **all** foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	almost daily
Yoghurt 290	❑	❑	❑	❑	❑	❑
Boiled or fried egg	❑	❑	❑	❑	❑	❑
Breakfast cereal/ oat meal, etc.	❑	❑	❑	❑	❑	❑
Dinner with						
- unprocessed meat	❑	❑	❑	❑	❑	❑
- sausage/meatloaf/ meatballs	❑	❑	❑	❑	❑	❑
- fatty fish (e.g. salmon/redfish) 295	❑	❑	❑	❑	❑	❑
- lean fish (e.g. cod)	❑	❑	❑	❑	❑	❑
- fishballs/fishpudding/fishcakes	❑	❑	❑	❑	❑	❑
- vegetables	❑	❑	❑	❑	❑	❑
Mayonnaise, remoulade	❑	❑	❑	❑	❑	❑
Carrots 300	❑	❑	❑	❑	❑	❑
Cauliflower/cabbage/ broccoli	❑	❑	❑	❑	❑	❑
Apples/pears	❑	❑	❑	❑	❑	❑
Oranges, mandarins	❑	❑	❑	❑	❑	❑
Sweetened soft drinks	❑	❑	❑	❑	❑	❑
Sugar-free ("Light") soft drinks	❑	❑	❑	❑	❑	❑
Chocolate	❑	❑	❑	❑	❑	❑
Waffles, cakes, etc. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	❑	❑	❑ 1
1-2 times a month	❑	❑	❑ 2
About once a week	❑	❑	❑ 3
2-3 times a week	❑	❑	❑ 4
More or less daily	❑	❑	❑ 5
	308		310

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 ..... ❑ 1
- A few times ..... ❑ 2
- 1-2 times a month ..... ❑ 3
- 1-2 times a week ..... ❑ 4
- 3 or more times a week ..... ❑ 5

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 ..... 314 _____ times
- later ..... 316 _____ times

If you have lost weight deliberately, about how many kilos have you ever lost at the most?

- before age 20 ..... 318 _____ kg
- later ..... 320 _____ kg

What weight would you be satisfied with (your "ideal weight")? ..... 322 _____ kg

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

- Never ..... 325 ❑ 1
- Not more than once a month ..... ❑ 2
- Two or more times a month ..... ❑ 3
- Once a week or more ..... ❑ 4

Your comments:

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 326 _____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? ..... 330 Yes ❑ No ❑

If "Yes", how many times? ..... 331 _____ times

If you still menstruate or are pregnant:

What date did your last menstruation period begin? 333 day/month/year ___/___/___

Do you usually use painkillers to relieve period pains? ..... 339 Yes ❑ No ❑

PREGNANCY

How many children have you given birth to? ..... 340 _____ children

Are you pregnant at the moment? ..... 342 Yes ❑ No ❑ Don't know ❑

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 343 Yes ❑ No ❑

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure 344	❑	❑
Proteinuria 346	❑	❑

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

Child	Year of birth:	Number of months breastfed:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

CONTRACEPTION AND ESTROGEN

Do you use, or have you ever used:	Now	Before	Never
Oral contraceptive pills (incl. minipill) ... 372	❑	❑	❑
Hormonal intrauterine device	❑	❑	❑
Estrogen (tablets or patches) 374	❑	❑	❑
Estrogen (cream or suppositories)	❑	❑	❑
	1	2	3

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

376 .....

If you use or have ever used oral contraceptive pills:

Age when you started to take the pill? ..... 380 _____years

How many years in total have you taken the pill? ..... 382 _____years

If you have given birth, how many years did you take the pill before your first delivery? ..... 384 _____years

If you have stopped taking the pill:

Age when you stopped? ..... 386 _____years

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

The Tromsø Health Survey

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