Diet, physical activity and venous thromboembolism

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A dissertation for the degree of Philosophiae Doctor

December 2013
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ACKNOWLEDGMENTS

The work of this thesis was carried out at the Hematological Research Group (HERG), Department of Clinical Medicine at the University of Tromsø, from August 2009 until December 2013. I started as a part of the MD PhD program for medical students (2009-2012), the final year I have been working as a PhD student financed by the Department of Clinical medicine, University of Tromsø and as an intern at the University Hospital of North Norway.

First, I would like to express my sincere gratitude to my excellent supervisor, Professor John-Bjarne Hansen. You convinced me to get into research, further you have guided me through four years of success and frustration, and taught me the joy of “pushing the submit button”. You impress me with your enormous knowledge, capacity and creativity. You are always available for supervision, and I always leave your office full of courage and inspiration.

Second, I would like to thank my equally excellent co-supervisor Sigrid Kufaas Brækkan. Your technical and statistical skills are invaluable. Your feedbacks are prompt, concise and thorough. You both have a wonderful spirit, and I value all our “out of office coffee breaks”. You and John Bjarne are the perfect supervisor-team! I also want to thank my co-authors Kristin Fjeldsa Enga, Tom Wilsgaard, Inger Njølstad, Ellisiv Mathisen Hald, Julie M. Süddduth-Klinger and Steven Watkins. I want to direct a special thanks to Tom and Kristin. Tom is our statistical guru, and it has been a big strength knowing that you have read through my articles with a statistical magnifying glass. Kristin is my very good friend and colleague. We have travelled this journey together; shared all of the good experiences and frustrations. I value all of our long and good talks, I cannot think of anyone I’d rather share this journey with! Furthermore, I would like to thank all current and previous members of HERG (Anders Vik, Ellen Brodin, Jan Brox, Bjarne Østerud, Arne Nordøy, Inger Marie Dahl, Tove Skjeldbakken, Birgit Svendsson, Mikhail Sovershaev, Elena Egorina, Timofey Sovershaev, Erin Mathisen Hald, Kristine Blix, Hilde Jensvoll, Gunhild Lerstad, Caroline Lind, Simin Jamalay, Irina Starikova, Trond Isaksen, Trond Børvik, Jostein Lappegård, Trygve Sølberg Ellingsen and Lars Daae Horvei) you are all important contributors to the great scientific and social environment in HERG.
I would like to use this opportunity to thank all of the participants in The Tromsø Study. We are proud of our high attendance rate, and your contribution is of course crucial for us to be able to do research.

Finally I would like to thank my family, for their love and encouragement and for always believing in me. Andreas, I could not have done this without you! Thank you so much for all those hours you have listened to me rehearsing, for always trying to help me solve problems I have encountered, and actually frequently being able to help!

Ida

Tromsø, October 2013
SUMMARY

There is substantial evidence for the influence of life-style factors on the incidence of arterial thromboembolic diseases such as myocardial infarction and stroke. However, limited knowledge exists on the relation between life-style factors and venous thromboembolism (VTE). VTE, a collective term for deep vein thrombosis and pulmonary embolism, is a common disease with serious short- and long-term complications including death. The aims of this thesis were to investigate whether life-style factors such as alcohol (type, amount, and drinking pattern), dietary pattern, fish consumption, and physical activity would influence the risk of VTE. We performed a population-based cohort study with participants from the Tromsø IV study. In the Tromsø IV study conducted in 1994-95, all inhabitants in the municipality of Tromsø aged 25 years or older were invited to participate and more than 27 000 attended (77% of the eligible population). Information was collected through questionnaires, blood samples and physical examinations. Incident VTE events were registered from inclusion (1994-95) until the end of follow-up, December 31 2010.

Total alcohol consumption was not associated with risk of VTE. However, intake of ≥ 3 units of wine per week lowered the risk of VTE by 22%, whereas intake of similar amount of liquor increased the risk of VTE by 50%. The beneficial effect of wine drinking was further strengthened (50% risk reduction) by adjustments for other types of alcohol (beer and liquor). Frequent binge drinking was also found to increase the risk of VTE. A heart-healthy diet was, as expected, associated with a lowered risk of myocardial infarction, but was not related to risk of VTE. Fish consumption was only associated with a non-significant, moderately reduced risk of VTE. However, the addition of fish oil supplements was associated with a 48% reduced risk. Immobility is a strong risk factor for VTE. Thus, we anticipated that regular physical exercise would protect against VTE. However, we found no association between the amount of regular physical activity at moderate intensity and the risk of VTE in the general population. However, high amounts of physical activity was associated with an increased risk in elderly and obese, whereas subjects younger than 60 years old and those normal-weighted (BMI≤25) had lower risk of VTE by increasing amounts of physical activity. Our findings imply that life-style factors have differential impact on arterial and venous thromboembolic diseases.
SAMMENDRAG

Vi har gjennomgående god kunnskap om hvordan usunn livsstil øker risikoen for arterielle tromboemboliske sykdommer som hjerteinfarkt og hjerneslag, men kunnskapen om effekten på risikoen for venøs tromboembolisme (VTE) er begrenset. VTE er et samlebegrep for blodpropp i kroppens dype vener (dyp venetrombose og lungeemboli). Målet med denne avhandlingen var å undersøke hvordan alkohol, diet, fiskekonsum og fysisk aktivitet påvirker risikoen for VTE i en generell befolkning.

Studiene er basert på den fjerde Tromsø undersøkelsen som ble gjennomført i 1994-95. Alle innbyggerne i Tromsø som var 25 år eller eldre ble invitert til å delta, og over 27 000 personer deltok. Informasjon om deltakerne ble samlet gjennom spørreskjema, blodprøver og klinisk undersøkelse. Deltakerne ble fulgt opp til utgangen av 2010, og alle VTE hendelsene ble registrert i oppfølgingsstiden.

Totalt alkoholkonsum var ikke assosiert med risiko for VTE, men å drikke 3 eller flere glass vin per uke var assosiert med 22 % lavere risiko for VTE. Denne assosiasjonen var enda mer framtredende i analyser hvor man også hadde justert for inntak av andre alkoholholdige drikker. Høyt sprit inntak var assosiert med 53 % høyere risiko for VTE. Overdrevent alkoholforbruk (mer enn 1 flaske vin, 4 flasker øl eller en kvart flaske sprit på en kveld) var også forbundet med økt risiko for VTE. Som forventet fant vi at et usunt kosthold var assosiert med høyere risiko for hjerteinfarkt. Vi fant imidlertid ingen sammenheng mellom kostvaner og risiko for VTE. Økt fiskekonsum var bare assosiert med en moderat, ikke signifikant lavere risiko for VTE, mens tillegg av fiskeolje var assosiert med en 48 % lavere risiko.

Vi fant ingen sammenheng mellom tid brukt til fysisk aktivitet av moderat intensitet og risiko for VTE. Mengden fysisk aktivitet av moderat intensitet var derimot assosiert med høyere risiko for VTE hos eldre (>60 år) og overvektige (Kroppsmasseindex (KMI) >30 kg/m²), og med lavere risiko for VTE blant personer yngre enn 60 år og normalvektige (KMI<25 kg/m²).

Våre funn tyder på at alkoholtyper og drikkmønster, samt fiskepising er assosiert med risiko for VTE, mens kostvaner forøvrig og fysisk aktivitet ikke vesentlig påvirker risikoen for VTE.
LIST OF PAPERS

The thesis is based on the following papers:

I. Alcohol consumption, types of alcoholic beverages and risk of venous thromboembolism – the Tromsø Study.
Hansen-Krone IJ, Brækkan SK, Enga KF, Wilsgaard T, Hansen JB. 

II. Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromsø Study.
Hansen-Krone IJ, Enga KF, Njølstad I, Hansen JB, Braekkan SK. 

III. Fish consumption, fish oil supplements and future risk of venous thromboembolism. The Tromsø Study.
Hansen-Krone IJ, Enga KF, Süddduth-Klinger JM, Mathiesen EB, Njølstad I, Wilsgaard T, Watkins S, Brækkan SK, Hansen JB. 
*Manuscript.*

IV. Physical activity and risk of venous thromboembolism. The Tromsø Study.
Borch KH, Hansen-Krone I, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. 
ABBREVIATIONS

AA: Arachidonic acid
ADH: Alcohol dehydrogenase
APC: Activated protein C
ARIC: Atherosclerosis Risk in Community
BMI: Body mass index
DASH: Dietary to Stop Hypertension
DVT: Deep vein thrombosis
COC: Combined oral contraceptives
CVD: Cardiovascular disease
ECG: Electrocardiogram
EPA: eicosapentaenoic acid
EPCR: Endothelial protein C receptor
Erg-1: Early growth response-1
FVII: Factor VII
FVIII: Factor VIII
HbA1c: Glycosylated haemoglobin
HIF-1: Hypoxia induced factor-1
HR: Hazard ratio
HRT: Hormone replacement therapy
IWHS: Iowa women’s health study
MI: Myocardial infarction
n-3 LCPUFA: n-3 long chained polyunsaturated fatty acids
OC: Oral contraceptives
OR: Odds ratio
PAI-1: Plasminogen activator inhibitor-1
PE: Pulmonary embolism
PTS: Post thrombotic syndrome
RCT: Randomized controlled trial
RR: relative risk
SIT: Seated immobility thromboembolism
SNPs: Single nucleotide polymorphisms
TF: Tissue factor
TFPI: Tissue factor pathway inhibitor
t-PA: tissue plasminogen activator
U.S.: United States
VTE: Venous thromboembolism
vWF: von Willebrand Factor
WC: Waist circumference
WHO: World Health Organization
1. INTRODUCTION

1.1 Epidemiology of venous thromboembolism

Venous thromboembolism (VTE), comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common life-threatening cardiovascular disease [1]. The annual incidence of VTE is estimated to be 1-2 per 1000 [2, 3]. DVT is the formation of a blood clot occurring in the deep veins, predominantly in the legs, but it can also occur in other parts of the body. PE is a potentially life-threatening complication of DVT. A PE occurs when a clot breaks free (embolization) and travels to the arteries of the lungs. About two-thirds of the VTE-events manifests as a DVT, and one-third as a PE with or without a concomitant identified DVT [4].

Death is one of the major outcomes of VTE. The one-month mortality rate has been reported to be 5-10% after first-time DVT and 8-16% after first-time PE [3, 5, 6]. However, mortality rates are lower among subjects with unprovoked events, and highest among cancer patients experiencing a VTE [7]. Within 1-2 years after a VTE, 15-50% develop the post-thrombotic syndrome (PTS) represented by chronic pain and swelling [8-10]. Moreover, severe PTS, characterized by intractable swelling, ulcerations and debilitating pain, appears in 5-10% of DVT patients [8, 11]. Of those with treated PE, 3-5% develop pulmonary hypertension [12, 13], and about 20% experiences a recurrent VTE within 5 years after the first DVT [14]. Interestingly, studies have shown that patients initially diagnosed with DVT are more likely to develop a recurrent DVT rather than PE. Similarly, those who are initially diagnosed with PE are more likely to develop a recurrent PE [15, 16].
1.2 Pathophysiology of venous thromboembolism

Virchow’s triad (figure 1), postulated by Rudolph Virchow in the mid-1800s, includes (i) blood stasis, (ii) hypercoagulability and (iii) changes in the vessel wall. These factors represent the most important contributors to development of thrombosis. Although it has been debated whether Virchow was actually the first to present this triad [17], it has for decades been the cornerstone of understanding the pathophysiology of VTE. Today we have knowledge about many factors contributing to the risk of VTE, nearly all of which can fall into one or more of the three factors of Virchow’s triad.

Figure 1) Virchow’s triad, illustrating the three most important factors contributing to the development of thrombosis.

The venous valves are essential for the blood circulation in the legs. However, they are also a frequent location for thrombosis initiation [18-20]. The endothelial cell surface contains natural anticoagulant components like thrombomodulin, endothelial protein C receptor (EPCR), tissue factor pathway inhibitor (TFPI) and heparin like proteoglycans. The concentration of these proteins is determined by the ratio of the endothelial cell surface to the blood volume, and is considerably higher in the microcirculation [21]. The efficacy of these
natural anticoagulants increases dramatically when the blood moves from the larger vessels to the microcirculation [22, 23]. Contrast media has been shown to linger in the valve sinuses of the larger vessels for an average time of 27 minutes during venography [24], apparently because of stasis which can be mediated through e.g. obesity, pregnancy and immobilization. Due to impaired natural mechanisms controlling the coagulation in the large vessels, the risk of developing thrombi will increase when the residence time of the blood in the large vessels increases as a result of stasis.

According to Sevitt et al. [18] vessel wall injury is seldom proven to be the cause of venous thrombi, except for when associated with acute insults like surgery or trauma. They also revealed that most venous thrombi consisted of two regions. One which mainly consisted of fibrin and trapped erythrocytes, while the other part mainly consisted of aggregated platelets. Moreover, they found that it was the fibrin-rich area that attached the thrombi to the vessel wall, suggesting that the activation of the coagulation system precedes the platelet activation. Tissue factor initiates the coagulation cascade on activated platelets, but TF is generally not expressed by endothelial cells under normal conditions [25]. Nevertheless, hypoxia associated with stasis has been shown to activate hypoxia induced factor-1 (HIF-1) and early growth response-1 (Erg-1) pathways [26, 27]. Both of these factors promote endothelial activation and permeability. In addition, activated monocytes are recruited. They produce TF-bearing microvesicles which can bind to P-selectin expressed on the activated endothelial cells, and initiate coagulation and thrombosis [28]. The response of HIF-1 and Erg-1 is proportional to the severity and duration of hypoxia. [29]. Furthermore, the anatomical location of severe, stasis-associated hypoxia has been shown to coincide with the anatomical location of thrombus initiation [18]. Studies have suggested that TF released by TF-bearing microvesicles are central in the pathogenesis of DVTs [28, 30]. Lastly, additional
platelets may be recruited to the fibrin clot rich in thrombin, and later contribute to further thrombus growth [28].

Cancer represents a hypercoagulable state. Cancer patients have elevated plasma clotting factors [31, 32] and higher levels of tissue factor (TF) [33]. Also thrombophilia and pregnancy are conditions contributing to hypercoagulability. During pregnancy there is a substantial increase in clotting factors [34], and inherited thrombophilias exerts their effect by disturbance of the endogenous anticoagulant system [35]. However, hypercoagulable states often need the facilitation of stasis to result in a thrombus [36].

1.3 Risk factors

VTE is a multicausal disease, affected by both acquired and inherited risk factors [37]. As many of the known risk factors such as advanced age, immobility, surgery and obesity are increasing in the society, VTE grows as an important public health problem [38]. Ethnic differences in the prevalence of VTE have been identified. Heit et al. [39] found a higher prevalence of unprovoked VTE among African-Americans. However, the prevalence of common acquired risk factors was low in this population. In addition, the frequency of the two most common inherited risk polymorphisms (factor V Leiden and prothrombin G20210A) was also low in African-Americans. This suggests that other, yet unrecognized, inherited polymorphisms could be associated with VTE in this group.

1.3.1 Inherited risk factors

Thrombophilia means a tendency to venous thrombosis [37]. Family studies [40, 41] have shown that genetic factors accounts for about 60% of the variation in susceptibility to thrombosis. Thrombophilia is generally divided into two groups. Group one contains inherited
deficiency of coagulation inhibitors, such as antithrombin and protein C and protein S deficiency. These are rare, but yield a high risk of thrombosis. Group two contains hereditary disorders associated with increases in levels or function of the coagulation factors, such as factor V Leiden, prothrombin gene mutation, elevated levels of coagulation factors (FVIII, IX and XI) and non-O blood groups. These are more common than the deficiencies in group one, but are associated with a lower risk of VTE [42]. In 1965, Egeberg [43] published the first description of a family with a hereditary tendency to venous thrombosis. Family members had reduced levels of antithrombin and recurrent episodes of VTE. Antithrombin inhibits thrombin (factor IIa), factor IXa, Xa, XIa and XIIa [44], and reduced levels of antithrombin yields reduced inhibition of these factors and hence increased coagulation. It is a rare deficiency, occurring in about 0.2% of the general population and in 0.5-7.5% of patients presenting with VTE [42]. Protein C deficiency associated with VTE was first described in 1981 [45]. With protein S as a cofactor, protein C inactivates factor Va and VIIIa. It occurs in about 0.2% of the normal population and in 2.5-6% of patients with VTE [42]. Three years later protein S deficiency was also described [46, 47]. Naturally, protein S deficiency also results in impaired inactivation of factors Va and VIIIa. It occurs in 1.3-5% of patients with VTE, whereas the frequency in the general population is unknown. All of the above described deficiencies increase the risk of VTE by approximately 10-fold in heterozygous carriers [48].

Resistance to activated protein C (APC), caused by an Arg506Gln mutation on human factor V (factor V Leiden), is the most frequent thrombophilic state present in about 5% of the healthy population and in 10% of patients presenting with VTE [42]. However, the frequency varies with ethnicity, as it is more common among whites and nearly absent among African-Americans [49, 50]. Despite being common, it yields a relatively low risk of VTE. In a large cross-sectional study [51], carriers of factor V Leiden had a 3-fold increased risk of VTE. Moreover, only 6% of the carriers had experienced a VTE by the age of 65, with most
thrombotic events occurring during high risk periods, such as after surgery [51]. Though, this prevalence is low compared to other studies [52, 53] which reported that VTE-events occurred in 20-40% of heterozygous carriers and 40-70% of homozygous carriers. Also prothrombin gene mutation (G20210A) is quite common and occurs in about 4% of the healthy population and in 5-10% of patients presenting with VTE [42]. The risk of VTE is relatively low [54] in adults who are heterozygous for the prothrombin mutation the relative risk (RR) of DVT is 2- to 5-fold increased [55]. Similar to factor V Leiden it has an ethnic variability, and is not as common in patients with African or Asian descent [56].

It is unknown why elevated levels of normal coagulation factors, such as factors VIII (FVIII), IX and XI, yields a higher risk of VTE, and also why they are elevated [42]. The risk estimates associated with elevated levels of coagulation factors are similar to the risks observed in patients with factor V Leiden and prothrombin mutation [42]. Non-O blood group as a risk factor for VTE is quite frequent (approximately 30%), but only yields an odds ratio (OR) for VTE of about 1.5-2. The increased risk of VTE associated with blood type A1 and B is partially explained by elevated coagulation factors (von Willebrand Factor (vWF) and FVIII), presumably because of decreased clearance [48].

As established in the family studies [40, 41] about 60% of the VTE-events are attributable to genetic factors. However, only one third (30%) of the events are explained by known thrombophilic factors [57]. This suggests that about 30% of the inherited risk factors are still not discovered. Several new susceptibility genes for VTE have been described after genetic research entered the “era of genome-wide association studies” (GWAS) [48]. The association between a huge number of single nucleotide polymorphisms (SNPs) with a phenotype have been tested, and new inherited variants identified. These risk factors are generally common in the population, but individually they yield only a modest increased risk of VTE, with OR ranging between 1.10 and 1.35 [48]. However, a recently published study
calculated a genetic risk score based on SNPs. This score was associated with VTE in a “dose-response” relationship, suggesting an additive effect of the risk alleles or genotypes.


1.3.2 Acquired risk factors

Advancing age is one of the best established risk factors for VTE. Several studies have found an exponential increase in VTE with increasing age [3, 59, 60]. A prospective study by Braekkan et al. [61] revealed an incidence rate of 5.7 per 1000 person-years among those aged ≥70 years old, whereas it was 2.5 for those aged 50-69 years and 0.5 for those <50 years of age (Figure 2). Increased levels of fibrinogen, factors VII, IX and other coagulation proteins, without a concomitant increase in anticoagulant factors, are likely to contribute to this increased risk [62]. Furthermore, studies have shown fibrosis and thickening in the valve leaflets and vein wall associated with increasing age [63, 64]. In addition, altered venous
blood flow due to (age-related) changes in compliance in the vein wall has been revealed [65]. Together these changes may affect the duration and frequency of stasis in the microenvironment of the venous sinus endothelium [29].

*Obesity* is an increasing problem, especially in Western countries. According to The World Health Organization (WHO) [66] over 1 billion people were overweight (defined as Body Mass Index (BMI) ≥25 kg/m²) and over 300 million people were obese (BMI ≥30 kg/m ) in 2005. By 2015 the number of subjects who are overweight will probably increase to at least 1.5 billion. The evidence of a relationship between BMI and VTE is strong, as illustrated by Ageno et al. in a meta-analysis [67]. They included 11 case-control studies [68-78] and two cohort studies [79, 80] and found a more than double risk of VTE for obese subjects (OR 2.33). Moreover, the association becomes stronger as the BMI increases [7], revealing a linear association between BMI and VTE. Several studies have also assessed the risk of VTE by other anthropometrical measures of overweight and obesity. A Swedish study followed 855 men aged ≥50 years in 1963 until they reached age 80 [81]. They found that subjects in the highest decile of waist circumference (WC) (≥100 cm) had an almost 4-fold increased risk of VTE (RR 3.92). A Danish follow-up from 2009 [82] found all measurements of obesity (body weight, BMI, WC, hip circumference and total body fat) to be equally good predictors of VTE. Similar risk estimates were published by Borch et al. [83] the following year. However, they found that WC yielded the highest risk and concluded that it was also the best anthropometric measure of obesity to identify subjects at risk of VTE [79]. Numerous possible mechanisms explaining the relationship between obesity and VTE have been proposed. Studies have shown that high BMI yields increased plasminogen activator inhibitor-1 (PAI-1) [84, 85], which compromise the normal clearance of fibrin and in turn promotes thrombosis [86, 87]. Also high levels of TF [88], fibrinogen and FVIII [89, 90] are associated with high BMI. Furthermore, it has been suggested that the hormone leptin, which
is produced in adipose tissue, and is increased in obese, might have prothrombotic effects due to its promotion of platelet aggregation [91]. Lastly, obesity leads to chronically raised intra-abdominal pressure and decreased blood velocity [62].

The association between cancer and VTE is well known, and the relation was actually first described around 1000 BC [92]. In 1980, Shen et al. [93] found that one of every seven hospitalized cancer patient died of PE and not of the cancer itself. Moreover, approximately 20% of all incident VTE-events are associated with malignancy [5, 60, 61, 94], and the relative risk of developing VTE is about four to seven times higher in patients with active cancer [95, 96]. In addition, cancer patients who develop VTE have about 3-fold higher risk of recurrent thrombosis compared to VTE patients without cancer [97]. Cancer is a hypercoagulable state and malignant cells can activate coagulation in numerous ways. Tumor cells produce procoagulant factors like tissue factor, cancer procoagulant and plasminogen activators [98]. Furthermore, they can express proteins that regulate the fibrinolytic system, including PAI-1 and urokinase-type and tissue-type plasminogen activators [99]. Tumor cells can also induce platelet activation and aggregation [100]. Also extrinsic factors associated with cancer contribute to an increased risk of VTE. White et al. [101] found an almost two-fold increased risk of VTE for cancer patients undergoing surgery. Moreover, stasis due to immobilization is one of the most frequent risk factors in non-surgical cancer patients [102]. In addition, stasis due to vascular invasion by the tumor also increases the risk of VTE [103]. Lastly, Heit et al. [104] found that cancer patients had a 7-fold increased risk of VTE. Furthermore, this risk increased to 10-fold for cancer patients receiving chemotherapy.

*Hospitalization* is a period where many risk factors for VTE (e.g. surgery, trauma, intravenous catheters, immobilization, pregnancy and chronic and acute medical conditions) may be present at the same time [38, 105]. However, hospital-acquired VTE-events can often be prevented by appropriate use of anticoagulant prophylaxis. In a nested case-control study,
Heit et al. [94] calculated that almost 60% of all incident VTE cases were attributed to hospitalization or nursing home residence. Of these, hospitalization with surgery counted for 24%, other hospitalizations for 22% and nursing home residence for 13%. Furthermore, the analysis showed that only 9% of the hospitalized patients received anticoagulant prophylaxis at the time of venous thromboembolism onset. A meta-analysis [106] found that prophylactic anticoagulant therapy was associated with a 39% reduced risk of non-fatal PE and a 53% reduced risk of symptomatic DVTs. Recently the U.S. Department of Health and Human Services expressed the need to promote implementation of evidence-based prevention strategies to reduce the number of preventable cases of VTE among hospitalized patients [107]. In the current American College of Chest Physicians (ACCP) guidelines [106], they recommend using the Padua Prediction Score to assess baseline risk of VTE. In this model high risk of VTE (11%) is defined by a cumulative score of ≥4 points, based on assigned points to 11 common risk factors [108].

The risk of VTE after surgery is well established, and recommendations of prophylactic anticoagulant therapy before surgery was suggested already in 1959 [109]. The prevalence of non-symptomatic DVT after hip arthroplasty, knee arthroplasty and hip fracture surgery is 42-57%, 41-85% and 46-60%, respectively [110]. The current debate involves deciding the appropriate thromboprophylaxis, based on the thromboembolic risk and the bleeding risk associated with surgery [111, 112].

Numerous studies, both from the late fifties and recently published, have shown a relationship between immobilization and VTE [113-117]. In 1972, Warlow et al. [118] investigated the frequency of venous thrombosis following stroke. Non-symptomatic DVT occurred in 60% of those with a paralyzed leg, compared to only 7% of those with a non-paralyzed leg. They concluded that prevention of VTE could be desirable in patients with stroke. “Seated immobility thromboembolism” (SIT) was a phrase suggested in a case-control
study from 2010 [119] reflecting that the risk of VTE is increased also due to prolonged seated immobility at work (OR 2.8), as well as long distance air, car and train travel. Another case-control study revealed that the increased risk associated with traveling was not dependent on the types of transportation. The odds ratio for air travel was comparable with the odds ratios for traveling with car, bus or train. However, the risk was only increased for travels with a more than 10 hours duration (OR 2.5) [120].

Several studies have investigated the association between risk of VTE and current use of combined oral contraceptives (COC), and the finding of a statistical significant increased risk has been remarkably consistent, with risk estimates ranging between 2 and 11 [121]. Ethinylestradiol is presumably the main component responsible for the increased risk of VTE due to COC use, yielding a procoagulant increase and anticoagulant decrease. Especially protein S decreases shortly after intake [122]. In addition, the risk depends on the type of progesterone which is combined with ethinylestradiol, and the so called third- or fourth generation COCs yields the highest risk [122]. Furthermore, a meta-analysis revealed a doubled risk of VTE among current users of hormone replacement therapy (HRT), with the highest risk during the first year of use (RR 3.49) [123].

*Pregnancy* is a risk factor for VTE. A population-based cohort study [124] reported a 3.5-fold increased risk of VTE in the antepartum and an 11.9-fold increased risk in the postpartum period, compared to outside of pregnancy. As mentioned, pregnancy is a hypercoagulable state characterized by increased levels of clotting factors and impaired fibrinolysis [125]. Moreover, pregnancy may lead to venous stasis [126].

Traditionally, arterial cardiovascular diseases (CVD) and VTE are considered two different diseases with different risk factors, pathophysiology and treatment. However, this concept has been challenged over the last decade. In a study by Prandoni et al. [127] higher prevalence of carotid plaques was found in subjects with unprovoked DVT, compared to
subjects with provoked thrombosis and hospitalized controls. Subsequently, Hong et al. [128] found a higher prevalence of coronary artery calcium in VTE-cases compared to controls. Contrary to these findings, prospective studies found no association between increased carotid intima media thickness or presence of carotid plaque and the risk of VTE [129, 130]. However, studies have found that VTE is both a risk factor for myocardial infarction (MI) and stroke [131, 132]. Also, subjects suffering from peripheral arterial disease [133] and subjects with a first arterial event [130] have increased risk of VTE. It has been discussed if a possible link between venous and arterial thrombosis could be mediated through shared risk factors. Several studies have been conducted, comparing risk factors for CVD and VTE. Family history of MI has been shown to be associated with an increased risk of development of VTE [61, 134, 135]. However, apart from obesity and advancing age, few other risk factors have consistently been linked to both arterial and venous thrombosis [1, 59, 69, 70, 81, 136-140]. Still, there have been shown similarities in the treatment of the two diseases. The JUPITER study revealed that rosuvastatin, a statin traditionally used to treat high cholesterol to prevent CVD, also yielded a 43% reduction in venous thrombotic events [141]. This finding was supported by a recent meta-analysis, but it needs to be further confirmed by randomized controlled trials [142]. In addition, aspirin has shown a possible preventive effect on VTE [143], a finding that was recently confirmed by the WARFASA-investigators in a multicenter double-blind randomized controlled trial [144]. The ASPIRE-study [145], another recently published randomized controlled trial, did not find a significant reduction in the primary outcome of VTE with aspirin compared to placebo. However, in concordance with the WARFASA-investigators they found aspirin to reduce the rate of recurrent venous thromboembolism.

Despite many known inherited and acquired risk factors, 25-50% of all incident VTEs occur without any detectable provoking factors. In contrast to coronary artery disease (i.e.
myocardial infarction), the incidence of VTE has not declined during the last decades [2].

With this in mind, it is imperative to continue the effort to identify new risk factors for VTE.

1.3.2.1 Alcohol consumption and risk of venous thromboembolism

Alcohol is widely consumed all over the world. Although most adults drink at a low-risk level, it creates a significant public health and safety problem in almost all countries [146]. However, alcohol has also demonstrated beneficial effects. The association between alcohol consumption and arterial cardiovascular diseases has been extensively investigated, concluding that moderate alcohol consumption reduces the risk of CVD [147, 148]. Several studies have also indicated that alcohol affects numerous factors involved in haemostasis, such as lowering fibrinogen [149-151], factor VII (FVII), vWF and plasma viscosity [151]. In addition, alcohol inhibits platelet aggregation [152] and yields an increase in levels of tissue plasminogen activator (t-PA) [149, 150]. However, the beneficial effect of moderate alcohol consumption seems to disappear after episodes of heavy drinking, yielding increased risk of ischemic strokes and sudden death [153]. Still, the relationship between alcohol consumption and VTE is not well described, and the results from the existing studies are diverging.

Of the studies investigating the relationship between alcohol consumption and VTE (Table 1), two prospective cohorts found an inverse relationship [154, 155]. The only study investigating the impact of different alcohol types and risk of VTE is the Iowa Women's Health Study (IWHS) [156]. They reported an observed protective effect of total alcohol consumption and beer consumption, but no association between wine or liquor and risk of VTE. A large Dutch study [157], found that subjects with a history of previous VTE had a lower alcohol intake than controls. Furthermore, they found 2-4 glasses per day to yield the greatest risk reduction. An additional finding was that alcohol consumers had a concomitant
decrease in fibrinogen [154]. This was suggested as an explanation for the decreased risk of VTE associated with increased alcohol consumption. In contrast, a French case-control [158] and two US prospective cohort studies [1, 59] found no association between alcohol and VTE.

Table 1. Observational studies investigating the relationship between alcohol consumption and VTE

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pahor (1996) [154]</td>
<td>Prospective</td>
<td>Women &gt;68 years</td>
<td>7 959</td>
<td>Low to moderate alcohol consumption is associated with a 60% reduced risk of VTE</td>
</tr>
<tr>
<td>Samama (2000) [158]</td>
<td>Case-control</td>
<td>Men and women Mean age: 59.1 (cases) 58.1 (controls)</td>
<td>636/636</td>
<td>No association between alcohol and VTE</td>
</tr>
<tr>
<td>Tsai (2002) [59]</td>
<td>Prospective</td>
<td>Men and women 45-64 years</td>
<td>19 293</td>
<td>No relationship between arterial risk factors (including alcohol) and risk of VTE</td>
</tr>
<tr>
<td>Glynn (2005) [1]</td>
<td>Prospective</td>
<td>U.S. male physicians 40-84 years</td>
<td>18 662</td>
<td>Daily alcohol consumption protects against CVD, but show no relation to VTE</td>
</tr>
<tr>
<td>Pomp (2007) [157]</td>
<td>Case-control</td>
<td>Men and women 18-70 years</td>
<td>4 423/5 235</td>
<td>2-4 glasses of alcohol per day yielded a 33% reduced risk of VTE</td>
</tr>
<tr>
<td>Lindqvist (2008) [155]</td>
<td>Prospective</td>
<td>Women 25-64 years</td>
<td>29 518</td>
<td>Moderate alcohol consumption (10-15 g/d) yielded a 60% lower risk of VTE</td>
</tr>
<tr>
<td>Lutsey (2009) [156]</td>
<td>Prospective</td>
<td>Women 55-69 years</td>
<td>37 393</td>
<td>Intake of alcohol ≥7/week yielded a 27% lower risk of incident VTE</td>
</tr>
</tbody>
</table>
1.3.2.2 Diet and risk of venous thromboembolism

In 1952 Jensen [159] reported a decrease in postoperative thromboembolism in Norway during the Second World War. He eliminated several possible explanations for the decrease, and finally concluded that the altered diet during the war years (1940-45), was presumably the most important factor. Because of war-restrictions, the diet in the Norwegian population was low in meat, high fat dairies, eggs, fruit, berries, sugar and coffee, and high in vegetables and fish [160]. Lately, articles have pinpointed that studying dietary patterns have greater value than studying isolated nutrients because people usually have complex diets, and nutrients may have synergistic effects [161]. The association between diet and arterial cardiovascular diseases has been thoroughly investigated. Healthy dietary patterns (often characterized as a Mediterranean diet) have been strongly associated to reduced risk of CVD [162, 163], still very little is known about dietary patterns and risk of venous thromboembolism.

Diet has been shown to affect several haemostatic factors. Mezzano et al. [164] found that subjects on a high fat diet had higher concentrations of fibrinogen, FVII and FVIII and lower levels of natural anticoagulants like antithrombin, protein C and protein S. Moreover, subjects on a healthy Mediterranean diet had high levels of antithrombin, protein C and protein S, and low levels of FVIII and PAI-1. Correspondingly, Weststrate et al. [165] found that subjects on low fat diet had lower levels of FVII and PAI-1. These factors are all related to VTE in varying degrees [166-170].

To the best of our knowledge, only four studies are published on the association between isolated nutrients or dietary patterns and risk of venous thromboembolism (Table 2). In the LITE-study [171], a diet including more plant foods and fish and less red and processed meat was associated with a lower incidence of VTE. Using principal component analysis, dietary patterns were identified. Analyses revealed a non-significant protective effect among those with the highest prudent dietary scores (high consumption of fish, fruit and vegetables) and a
significant increased risk associated with high western dietary score (high consumption of red processed meat and saturated fat) [168]. In the Iowa Women's Health Study (IWHS) [156] they also studied isolated nutrients and dietary patterns, identified by factor analysis, but their conclusion was not in concordance with LITE. In the IWHS, the prudent pattern was characterized by high intake of vegetables, fruit and poultry, whereas the western pattern had a greater intake of processed meat, non-cereal whole grains, added fats and oils. They found no association between either prudent or western dietary patterns and risk of VTE [153]. A population based case-control study conducted on a Thai population [172] found that subjects experiencing a VTE had a lower intake of vegetables, fish and spicy food. However, only vegetables were significantly associated with risk of VTE in multivariate analysis. Recently a large prospective study [173] found no association between a prudent dietary pattern and VTE, but found a weak increased risk of VTE for those with a Western dietary pattern.

The IWHS discussed possible explanations for the diverging results in their study compared to the LITE-study [156]. One explanation could be that the study population in IWHS was older than in LITE, and increasing age can lead to a change in metabolism, decline in nutrient absorption and attenuated kidney function and energy needs [156]. Moreover, the follow-up in IWHS was 7 years longer than in LITE, which may have led to greater dietary misclassification in the older IWHS-population. Furthermore, IWHS included 127 questions in their questionnaire, while LITE only included 66 questions. This may have led to LITE getting less extensive information, but maybe more accurate answers because it is easier to complete a shorter questionnaire.
Table 2.

**Observational studies on the association between diet and VTE**

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steffen (2007)</td>
<td>Prospective</td>
<td>Men and women 45-64 years</td>
<td>14 962</td>
<td>A western dietary pattern yielded a 60% increased risk of VTE</td>
</tr>
<tr>
<td>[171]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutsey (2009)</td>
<td>Prospective</td>
<td>Women 55-69 years</td>
<td>37 393</td>
<td>No independent association between diet and VTE</td>
</tr>
<tr>
<td>[156]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhoopat (2010)</td>
<td>Case-control</td>
<td>70% women, Mean age 54.6</td>
<td>97/195</td>
<td>More than 3-fold increased risk of VTE for those with a low consumption of vegetables</td>
</tr>
<tr>
<td>[172]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varraso (2012)</td>
<td>Prospective</td>
<td>Female nurses 30-55 years and Male US health professionals 40-75 years</td>
<td>129 430</td>
<td>Men with a western dietary pattern had a 43% increased risk of VTE (no associations in women)</td>
</tr>
<tr>
<td>[173]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.3.2.3 *Fish consumption and risk of venous thromboembolism*

A protective effect of fish consumption on cardiovascular diseases has consistently been shown in several studies over the past decades [174-178]. Others have also proven an additional effect of fish oil supplements [179, 180]. Already in 1978 Dyreberg et al. [181] published a study conducted on Greenland Eskimos. They found reduced platelet aggregability in this population and concluded that this was probably due to their diet, which mainly was of mammalian marine origin; rich in n-3 long chained polyunsaturated fatty acids (n-3 LCPUFAs). This diet led to a relative increase in the omega-3 eicosapentaenoic acid
(EPA) at the expense of the omega-6 arachidonic acid (AA) in platelets, resulting in reduced platelet aggregation [182].

Possible mechanisms for the protective effect of fish consumption on the risk of CVD have been studied. High fish intake have been shown to prevent arrhythmia [181, 183] and possibly yield plaque stabilization [184]. In addition, it has also been known to affect haemostatic factors, resulting in lower levels of fibrinogen, FVIII and vWF and higher levels of protein C [90]. A decreased expression of TF in monocytes [185] and endothelial cells [186] has also been associated with increased levels of n-3 LCPUFA.

Table 3.

Observational studies on the association between fish consumption and VTE

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steffen (2007) [171]</td>
<td>Prospective</td>
<td>Men and women 45-64 years</td>
<td>14 962</td>
<td>30-45% lower risk of VTE for subjects consuming fish ≥1/week</td>
</tr>
<tr>
<td>Lutsey (2009) [156]</td>
<td>Prospective</td>
<td>Women 55-69 years</td>
<td>37 393</td>
<td>22% increased risk of VTE for subjects consuming fish ≥2/week</td>
</tr>
<tr>
<td>Bhoopat (2010) [172]</td>
<td>Case-control</td>
<td>70% women, Mean age 54.6</td>
<td>97/195</td>
<td>No association between fish consumption and VTE</td>
</tr>
<tr>
<td>Varraso (2012) [173]</td>
<td>Prospective</td>
<td>Female nurses 30-55 years and Male US health professionals 40-75 years</td>
<td>129 430</td>
<td>No association between fish consumption and VTE</td>
</tr>
</tbody>
</table>
Few studies have investigated the relationship between fish consumption and VTE (Table 3). In the LITE-study [171] they found a 30-45% lower incidence of VTE in subjects consuming fish ≥1/week compared to <1/week, and a similar association between intake of omega-3 fatty acids as a nutrient and risk of VTE was also reported. Contrary, the IWHS [156] actually found an increased risk of VTE associated with a high weekly intake of fish (≥2 times/week). A Thai case-control study found an almost 3-fold increased risk of VTE for those consuming less than 0.42 servings of fish per day, this association disappeared in multivariable analysis and they concluded that fish consumption was not associated with risk of VTE. In the Nurses’ health study and Health Professionals Follow-up study [173], no association between fish consumption and risk of VTE was detected.

13.2.4 Physical activity and risk of venous thromboembolism

As Virchow postulated, blood stasis which can be caused by immobilization and physical restriction, was one of the main contributors to thrombotic disease. Muscle activity yields a distinct decrease in venous pressure, elevation of blood flow, and prevents edema [187-189]. Accordingly, it would be reasonable to believe that physical exercise would lower the risk of VTE. However, the results of the existing research are diverging (Table 4).

The MEGA-study [190] found that participating in sports activities regularly yielded a 29% reduced risk of VTE, compared to not participating in sports activities at all. They found no differences in risk estimates for various frequencies, intensities or types of sport. Another case-control study [191] found an increased risk of VTE associated with use of oral contraceptives, which were reduced among women who participated in regular and vigorous exercise. One of the main findings of a large prospective cohort [155] was that women who engaged in strenuous exercise (bicycling, gymnastics, dancing more than once a week) were at half the risk of VTE compared to women who led a sedentary lifestyle. Whereas walking
several times a week did not yield the same significant protective effect. Whilst the Physicians’ Health Study [1] found exercise to have a protective effect on CVD and stroke, it actually yielded an increased risk of VTE, particularly for provoked events. Similarly, a prospective study in elderly [192] found that mild-intensity exercise such as walking gave a non-significant beneficial effect, while strenuous exercise such as jogging was associated with a 75% greater risk of VTE compared to no exercise. The LITE-study [59] found no association between physical activity and VTE, but they did reveal a tendency of increased risk with increasing levels of activity.

### Table 4.

**Observational studies on the association between physical activity and VTE**

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsai (2002) [59]</td>
<td>Prospective</td>
<td>Men and women 45-64 years</td>
<td>19 293</td>
<td>No relationship between arterial risk factors (including physical activity) and risk of VTE</td>
</tr>
<tr>
<td>Glynn (2005) [1]</td>
<td>Prospective</td>
<td>U.S male physicians 40-84 years</td>
<td>18 662</td>
<td>Exercise protects against CVD and stroke, but is associated with a 9% increased risk of VTE</td>
</tr>
<tr>
<td>Sidney (2004) [191]</td>
<td>Case-control</td>
<td>Women 15-44 years</td>
<td>196/746</td>
<td>The increased risk associated with use of OR was 50% reduced among those who exercised vigorously</td>
</tr>
<tr>
<td>Van Stralen (2007) [190]</td>
<td>Case-control</td>
<td>Men and women 18-70 years</td>
<td>3 608/4 252</td>
<td>Regular sport activities yielded a 29% reduced risk of VTE</td>
</tr>
<tr>
<td>Van Stralen (2008) [192]</td>
<td>Longitudinal</td>
<td>Men and women &gt;65 years</td>
<td>5 534</td>
<td>Strenuous exercise was associated with a 75% higher risk of VTE</td>
</tr>
<tr>
<td>Lindqvist (2009) [155]</td>
<td>Prospective</td>
<td>Women 25-64 years</td>
<td>29 518</td>
<td>Physically active women were at a 60% reduced risk of VTE</td>
</tr>
</tbody>
</table>
2. **AIMS OF THE STUDY**

The aims were to use a large prospective, population based cohort-study to:

- Assess the impact of total alcohol consumption and different types of alcohol on the risk of venous thromboembolism.
- Investigate the association between a heart healthy diet and risk of myocardial infarction and venous thromboembolism in the same, general population.
- Assess whether fish consumption and fish oil supplements is associated with future risk of venous thromboembolism.
- Examine the relationship between regular physical activity and the risk of venous thromboembolism.
3. STUDY POPULATION AND METHODS

3.1 The Tromsø Study

The Tromsø Study was founded by the University of Tromsø in 1974. The aim was primarily to determine possible factors causing the high cardiovascular mortality, which was especially pronounced in the Northern part of Norway [193]. However, since then several other chronic diseases and conditions have been included in the study. Six surveys have been conducted, the first in 1974 and the last in 2007-08. They all have the same general design and is a combination of repeated health surveys and research conducted on a large, representative sample of the Tromsø population [193].

All four papers included in this thesis are based on the fourth survey of the Tromsø study (Tromsø IV). It was conducted in 1994-95, and is the largest of the six surveys. All inhabitants in the municipality of Tromsø aged ≥25 years were invited to participate, and 27 158 (77% of the eligible population) attended. Furthermore, all men and women aged 50-74 in the municipality, as well as smaller random samples (5-10%) of those aged 25-54 and 75-85 years old, were invited to a more extensive second visit. Of the 10 542 eligible subjects 78% (7965) attended the second visit.

3.2 Baseline measurements – (Tromsø IV)

Baseline information on cardiovascular risk factors was collected by physical examinations, blood samples, and self-administered questionnaires. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor), by specially trained personnel. Participants rested for 2 minutes in a sitting position, and then three readings were taken on the upper right arm, separated by 2-minutes intervals. The average of the two last readings was used in the analysis. Height and weight was measured with subjects wearing light clothing and no shoes. Body mass index was calculated as weight in kilograms, divided
by the square of height in meters (kg/m²). Waist circumference was measured at the umbilical line. Non-fasting blood samples were collected from the antecubital vein, serum prepared by centrifugation after one hour respite at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic, colorimetric methods and commercially available kits (CHOD-PAP for cholesterol, and GPO-PAP for triglycerides: Boering Mannheim). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Determination of glycosylated haemoglobin (HbA1c) in EDTA whole blood was based on an immunoturbidometric assay (UNIMATES, F. Hoffmann-La Roche AG: Basel, Switzerland). The HbA1c percent value was calculated from the HbA1c/haemoglobin ratio. Information on alcohol consumption, dietary habits and physical activity was collected from a self-administered questionnaire (Appendix), extensively described in papers I-IV. In order to assess dietary patterns (paper II) 37-dietary questions from the original questionnaire was transformed into a slightly modified version of the SmartDiet questionnaire (extensively described in paper II, Dietary assessment). This was further used to calculate a SmartDiet score for each individual (Table 1, paper II). Individual scores were finally divided into tertiles using computer software (SPSS).

3.3 Outcome measurements

3.3.1 Venous thromboembolism

All first lifetime events of VTE during follow-up were identified by searching the computerized index of medical diagnoses, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. The University Hospital of North
Norway is the only hospital in the Tromsø region, and all hospital care and relevant diagnostic radiology in the Tromsø community is provided exclusively by this hospital. The relevant discharge codes were ICD-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9, for the period 1994-1998, and ICD-10 codes I26, I80, I82, I67.6, O22.3, O22.5, O87.1, O87.3 for the period 1999-2010. The index of medical diagnosis included diagnoses from outpatient clinic visits and hospitalizations. An additional search through the computerized index of autopsy diagnosis was conducted, and cases diagnosed with VTE, either as a cause of death (part one on the death certificate), or as a significant condition (part two of the death certificate), were identified. We also searched the radiology procedure registry to identify potential cases of objectively confirmed VTE that may have been missed because of coding errors in the index of medical diagnose. All relevant diagnostics procedures performed at the Department of Radiology, to diagnose VTE during the 14-year period, were systematically reviewed by trained personnel, and cases with objectively confirmed VTE were identified.

The medical records for each potential VTE-case, derived from the medical diagnostic index, the autopsy registry, or the radiology procedure registry, were reviewed by trained personnel, who were blinded to the baseline variables. For subjects derived from the medical diagnostic index and the radiology procedure registry, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled; (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan or autopsy), (ii) the medical record indicated that a physician had made a diagnosis of DVT or PE, (iii) sign and symptoms consistent with DVT or PE were present and (iv) the patient underwent therapy with anticoagulants (heparin, warfarin, or a similar agent), thrombolytics or vascular surgery. For subjects derived from the autopsy registry, a VTE event was recorded as an outcome when the
autopsy record indicated VTE as cause of death or as a significant condition contributing to death.

3.3.2 Myocardial infarction

Adjudication of hospitalized and out-of hospital events of MI was performed by an independent endpoint committee and based on data from hospital and out-of hospital journals, autopsy records, and death certificates. The national 11-digit identification number allowed linkage to national and local diagnosis registries.

Cases of incident MI were identified by linkage to the hospital discharge diagnosis registry at the University Hospital of North Norway with search for ICD-9 codes 410-414 and 430-438 in the period 1994-1998 and thereafter ICD 10 codes 120-125, and I60-I69. The hospital medical records were retrieved for case validation. Slightly modified WHO MONICA/MORGAM [194] criteria for MI were used and included clinical symptoms and signs, findings in electrocardiogram (ECG), values of cardiac biomarkers and autopsy reports when applicable. Further, linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal incident cases of MI that occurred outside of Tromsø, as well as information on all-cause mortality. Information from the death certificates was used to collect relevant information of the event from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners.
MAIN RESULTS

4.1 Paper I:

ALCOHOL CONSUMPTION, TYPES OF ALCOHOLIC BEVERAGES AND RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

In this study we aimed to assess the impact of total alcohol consumption, and consumption of beer, wine and liquor on the risk of VTE in a large, prospective, population-based study. Alcohol consumption habits were obtained from a self-administered questionnaire filled out by 26,662 subjects aged 25-97 years, participating in the Tromsø study in 1994-95. First lifetime events of VTE were registered from the date of enrolment to September 1, 2007. During a median follow-up of 12.5 years, 460 incident VTE events were detected. Total alcohol consumption was not associated with risk of VTE. However, subjects with a wine consumption of ≥3 units/week had a 22% non-significant reduced risk of VTE (Hazard ratio (HR): 0.78, 95% CI: 0.47-1.30) compared to teetotalers in multivariable analysis adjusted for age, sex, BMI, smoking, diabetes, cancer, previous cardiovascular disease, physical activity and higher education. The association was strengthened by further adjustments for beer and liquor intake (HR: 0.53, 95% CI: 0.30-1.00). Contrary, subjects consuming ≥3 units of liquor per week had a 53% increased risk of VTE compared to teetotalers in multivariable analysis (HR: 1.53, 95% CI: 1.00-2.33). Frequent binge drinking (≥1/week) was also associated with increased risk of VTE (HR: 1.17, 95% CI 0.66-2.09), compared to teetotalers, and a 47% increased risk compared to non-binge drinkers (HR: 1.47, 95% CI: 0.85-2.54). This study indicates that wine consumption may be beneficial with regard to risk of VTE, while liquor consumption and binge drinking may yield an increased risk. More studies are needed to investigate the association between different types of alcoholic beverages and the risk of VTE.
HEART HEALTY DIET AND RISK OF MYOCARDIAL INFARCTION AND VENOUS TRHOMBOEMBOLISM – THE TROMSØ STUDY.

A heart healthy diet has consistently been associated with a reduced risk of myocardial infarction. We wanted to investigate the effect of a heart healthy diet on the risk of myocardial infarction (MI) and venous thromboembolism (VTE) within the same study population. We conducted a prospective cohort study, based on the Tromsø IV study (1994-95), including 18062 subjects, aged 25-70 years. From a 13-item questionnaire we calculated a dietary score based on the participants intake of fat, fiber, fruit and vegetables. The score is a modified version of the validated SmartDiet score. During a median follow-up of 10.8 years, 518 incident MIs and 172 incident VTEs were identified.

A heart healthy dietary score (>27) was associated with a 17% reduced risk of MI, compared to those who had an unhealthy score (<25) (HR: 0.83, 95% CI: 0.66-1.06) in multivariable analysis adjusted for age, sex, BMI, physical activity, smoking, self-reported diabetes, history of other CVD (angina pectoris and stroke) and history of cancer. However, a heart healthy dietary score was not associated with the risk of VTE (HR: 1.01, 95% CI: 0.66-1.56). High intake of fish, fruit, vegetables and polyunsaturated fat resulted in a 23% reduced risk of MI (HR: 0.77, 95% CI: 0.64-0.98), but was not associated with VTE (HR 0.95, 95% CI: 0.64-1.40). A risk reduction of 38% for MI (HR 0.62, 95% CI: 0.41-0.95) was found in obese subjects (BMI ≥30 kg/m²) consuming a heart healthy diet, whereas there was no risk reduction for VTE in the same population (HR: 1.10, 95% CI: 0.53-2.27). In conclusion, we detected an expected moderate protective effect of a heart healthy diet on the risk of MI, but found no association between the same diet and the risk of VTE.
4.3 **Paper III:**

**FISH CONSUMPTION, FISH OIL SUPPLEMENTS AND FUTURE RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY.**

Fish consumption and fish oil supplements are known to have many beneficial effects on cardiovascular risk. It reduces platelet aggregability, lowers triglyceride levels and has several antithrombotic effects on haemostatic factors. Current knowledge of the effect of fish consumption on risk of venous thrombosis is scarce and diverging. Therefore, we wanted to investigate the association between fish consumption and risk of venous thromboembolism, and included 23 621 subjects aged 25-97 years participating in the Tromsø IV study (1994-95). From the date of enrollment to the end of the study period (October 31, 2010), 536 incident VTE events occurred.

A high weekly consumption of fish (≥3/week) was associated with a moderately reduced risk of VTE (HR 0.78, 95% CI; 0.60-1.01) compared to a moderate fish consumption (1-1.9/week) in multivariate analysis adjusted for age, BMI, sex, HDL-cholesterol, physical activity and education level (education at university/college level). The addition of fish oil supplements strengthened this effect (HR: 0.52, 95% CI: 0.34-0.79). In separate analysis of fatty and lean fish, a lean fish consumption of ≥2/week was associated with an 11% lower risk (HR: 0.89, 95%CI; 0.73-1.08) of VTE compared to those who consumed lean fish 1-1.9/week. Those who consumed fatty fish ≥2/week had a 20%, lower risk of VTE (HR: 0.80, 95% CI: 0.59-1.08), and the combination of a high fat fish consumption and fish oil supplements was associated with 50% lower risk of VTE (HR: 0.50, 95% CI: 0.29-0.88) compared to those with a moderate fat fish consumption and no use of fish oil supplements.

In conclusion, a high weekly intake (≥3/week) of fish for dinner was associated with a moderately reduced risk of VTE. Further studies are needed to confirm the inverse association between fish consumption and risk of VTE.
4.4 Paper IV:

PHYSICAL ACTIVITY AND RISK OF VENOUS THROMBOEMBOLISM. THE TROMSØ STUDY.

Regular physical activity is inversely associated with the risk of arterial cardiovascular diseases. The aim of this study was to assess the impact of regular physical activity on the risk of VTE in 26,490 subjects aged 25-97 years, participating in the Tromsø IV study in 1994-95. From the date of enrollment to the end of the study period, September 1, 2007, 460 incident VTE events were detected.

No significant association between regular physical exercise of moderate intensity (1.0-2.9 hours/week) and VTE was detected. On the other hand, high intensity exercise (≥3 hours/week) in elderly (≥60 years) was associated with increased risk of provoked (HR: 1.30, 95% CI: 0.84-2.00) and total VTE (HR: 1.33, 95% CI: 0.80-2.21) compared to inactivity (0 hours/week) in the multivariable model adjusted for age, gender, BMI, diabetes and smoking. Also obese subjects (≥30 kg/m²) engaged in high intensity exercise had increased risk of VTE (HR: 1.49, 95% CI: 0.63-3.50). Contrary, moderate physical activity was associated with reduced risk of VTE in subjects under 60 years (HR: 0.72, 95% CI: 0.48-1.08) and in subjects with BMI < 25 kg/m² (HR: 0.59, 95% CI: 0.35-1.01) compared to inactivity. In conclusion, physical activity was not associated with the risk of VTE in a general population.
5. GENERAL DISCUSSION

5.1 Methodological considerations

Study design

Prospective cohorts have several advantages compared to other study designs. Entire populations are often invited to participate, making cohorts well suited to investigate common diseases. Contradictory, a case-control study design includes only participants with a certain disease and eligible controls. This design is more efficient for investigating rare diseases. In the Tromsø IV Study, which all four papers included in this thesis are based on, all inhabitants of the municipality of Tromsø aged ≥ 25 years old were invited to participate. Including whole populations increases the external generalizability and the chance of finding a valid association. Furthermore, the prospective cohort design is a valid method for providing reliable estimates of future outcome probability (true risk prediction), which is based on the currently observed exposure to multiple risk factors [195]. The prospective design is characterized by a temporal sequence of exposure and outcome, which is essential to establish causality [196]. Contrary, case-control studies are often referred to as retrospective, tracing backwards from outcome to exposure, seeking to reveal the frequency of exposure to a risk factor in cases compared to controls. This retrospective study design is more prone to temporal bias (or reversed causality), as it is not always clear that the exposure preceded the diagnosis of the disease of interest. Retrospective report of information also increases the risk of recall bias. A new diagnosis may affect the memory of the cases in several ways. It may be enhanced, because cases may be more likely to search for explanations for their disease, and therefore assign more significance to past events or exposure. Contrary, the memory may be reduced or even clouded. Because these errors are dependent on the outcome variable, which is affecting their memory, it is characterized as a differential misclassification. This kind of differential misclassifications frequently leads to an overestimation of the measured effect.
The non-temporal nature (Recall bias) is one of the main reasons why the estimates provided by case-control studies generally are regarded less valid than measurements obtained from cohort studies. Furthermore, selection of controls can also be problematic in case-control studies since the validity of these studies depends on selecting appropriate control groups. Ideally, selection should involve direct sampling of controls from the source population of cases, rather than from the entire non-diseased population [197]. Several methods for recruitment of controls have been developed, like neighbor- or spouse recruitment. Both of which may cause selection bias due to “mating”, i.e. the cases and controls are too similar in factors like IQ, age, education, and socioeconomic status. Because of its limits, case-control studies cannot prove a cause-and-effect relationship, but it can generate a hypothesis of causality. However, case-control studies have some advantages. Obviously, they are more efficient and less expensive than cohorts, and they are better suited to investigate rare diseases and studies of genetics.

Randomized controlled trials (RCTs) are the gold standard for research in modern medicine, aiming to reveal a cause-and-effect relationship. Participants are randomized into two groups: one group receives active treatment (or other interventions), the other group is the control group receiving either no treatment or placebo. Under these conditions it is possible to control both biases and confounding, and obtain a more valid risk reduction measurement. A drawback of RCTs is that they are expensive and time consuming, and due to the strict inclusion criteria the generalizability is attenuated. In addition, RCTs may be ethically problematic. An RCT of alcohol intake to test the hypothesis of a protective effect of wine consumption on VTE is unlikely to be conducted.

Mendelian randomization is a method for assessing the causal nature of some environmental exposures or biomarkers. These studies are considerably less prone to confounding than observational studies [198]. The variation in genes of known functions is
used to examine the causal effect of a modifiable exposure on disease. Recently a study [199] used mendelian randomization to test the hypothesis that genetically raised plasma HDL cholesterol might be protective of myocardial infarction. They used the genome-wide association approach to identify SNPs that affect blood lipid concentrations. A SNP in the endothelial lipase gene (LIPG Asn396Ser) was tested in 20 studies. Carriers of the allele had higher HDL cholesterol, but similar levels of other lipids and non-lipid risk factors for MI, compared with non-carriers. Furthermore, they used a genetic score consisting of 14 common SNPs that are exclusively associated with HDL cholesterol and tested this score in cases and controls. Finally, they used a genetic score of 13 common SNPs exclusively associated with LDL cholesterol as a positive control. An increase of 1 standard deviation (SD) in HDL due to genetic score was not associated with risk of MI. Contrary, they found increased LDL to increase the risk of MI using the genetic score. These findings challenge the concept that raised plasma HDL is a marker for reduced risk of MI. Possible limitations to the mendelian randomization design is that the effect sizes are likely to be small, suitable polymorphisms to study certain exposures may not be available and there is still a small risk of confounding [198].

Sir Austin Bradford Hill [196] discusses nine aspects which should be carefully considered before deciding whether or not an observed association is causal. Eight of them (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence and analogy) are possible to encounter within the frames of the prospective cohort study design. However, the criteria of experimental evidence for the detected association, is not possible within this design. It would therefore be optimal to test the associations found in prospective cohorts, i.e. a reduced risk of VTE due to intake of fish oil supplements, by subsequently conducting a RCT. In an RCT the intervention group would receive fish oil supplements and
the control group would receive placebo, revealing the true effect of fish oil supplements on the risk of VTE.

**Generalizability**

It is a great advantage to be able to study associations between exposure and diseases in large, general populations, because biological effects may differ between populations and different subgroups. As previously mentioned, The Tromsø IV Study is a large cohort comprising 27,158 men and women aged 25-97 years old. With an attendance rate of 77%, we believe that this cohort is quite representative for the population of Tromsø, which in turn does not differ greatly from other Western populations in terms of distribution of risk factors [5, 60]. However, there might be a difference between the 77% who attended and the 23% who did not, since people of good health are more prone to participate in health surveys. This may cause bias due to self-selection. In cohort studies participants are selected before the disease actually occurs, bias will then often affect both exposed and unexposed equally. The result is therefore generally not affected. However, overrepresentation of healthy participants can lead to detection of fewer cases, which may lead to less power and ability to detect an association. There was a somewhat higher attendance rate among women aged 55-59 in The Tromsø IV study, but overall there was no difference between men and women. However, the attendance rate was lower among those <40 and those >80 years old, risking slightly impaired generalizability for these age groups.

**Confounding**

The concept of confounding have for centuries been discussed by philosophers and scientists. Confounding can informally be described as a confusion of effects, or a mixing of effects of extraneous factors (confounders) with the effect of interest [200]. A more precise
definition is a situation in which the study exposure group differ in their probability distribution for the outcome, for reasons other than the effects of exposure [201].

Furthermore, the confounding factor has to be related to the outcome variable and associated to the exposure variable, but it shall not be an intermediate factor or a result of either the exposure or outcome [202]. An example on confounding is taken from paper III, regarding the relation between fish consumption, age and VTE. In our population the consumption of fish is far more frequent among the elderly participants than among the younger participants, and we know that age is a strong risk factor for VTE. In crude analysis on the association between fish consumption and VTE, increasing consumption yielded an overwhelmingly increased risk of VTE. This association completely disappeared after the adjustment for age because age was a confounding factor.

There are several strategies for dealing with confounders. One of the most effective is restriction [200]. If there is a gender imbalance a solution could be to restrict the analysis to women or men only. However, restrictions can both reduce the number of available subjects to unacceptably low levels and it can reduce the generalizability. This can further be avoided by matching the comparison groups, but matching can in turn lead to selection bias. The simplest method is to stratify for confounders, e.g. analyses could be done separately for different genders, age groups etc. Again, one can encounter the problem of sparse data in the separate analyses.

In paper I-IV we have dealt with confounders by adjusting for them in multivariable analysis. Inclusion of several variables in this manner secures that each term is unconfounded by the other terms. Nevertheless, one can never rule out the possibility of residual confounding. In addition, insufficient data makes it impossible to adjust for some known risk factors. In our study we lack baseline information on inherited thrombophilia. However, information on thrombophilic factors was collected at the time of the VTE event. Only 16%
of those with an unprovoked event had one or more known thrombophilic factors registered. Accordingly, the majority of the unprovoked events were probably caused by other unknown risk factors. Furthermore, to the best of our knowledge, no studies are published revealing synergistic effects between any of the risk factors in paper I-IV and thrombophilia. Consequently, the risk of inherited thrombophilia representing unrecognized confounders in our study is diminished.

**Self-administered questionnaires and Misclassification**

Self-administered questionnaires are widely used to collect information on large study populations, and it is the method used to collect data in all four papers included in this thesis. This method has been criticized, and the validity of the data collected in this matter questioned. It has been argued that it is hard to monitor, and that the risk of misunderstanding of questions and skipped answers is present to a larger extent than in interviewer-administered questionnaires. However, there are many advantages in using self-administered questionnaires, especially when collecting data from large cohorts. Obviously it costs less and is a more efficient method. Also, it may be more accurate in collecting data on sensitive and embarrassing topics (e.g. mental health, sexuality and sexual behavior). Furthermore, a study comparing information between self- and interviewer-administered questionnaires on lifestyle habits [203] concluded that the two methods yielded very similar results, but in the interviewer-administered questionnaires the participants tended to systematically give responses that were considered more socially acceptable. This finding is in accordance with previous studies [204], and some have actually concluded that self-administered questionnaires have a higher degree of validity and accuracy [205-207].

When collecting information from a large population, one always runs the risk of misclassification due to information bias. Such misclassifications can be differential or non-
differential. If the misclassification of an exposure differs between those with and without disease, it is classified as differential. Contrary, if the misclassification is independent of the outcome variable, it is classified as non-differential. Collecting information at baseline, as is done in prospective cohorts, reduces the possibility of a misclassification being dependent on the outcome variable, and is therefore generally non-differential. Contrary to differential misclassifications, this usually leads to an underestimation of the true association. As previously discussed, self-administered questionnaires are considered a valid method for gathering information on lifestyle factors. Another method for validating information collected through questionnaires is detecting expected effects of our exposure variables on other factors. We found a protective effect of a heart healthy diet on myocardial infarction, a decrease in triglycerides with increasing fish consumption, and increasing concentration of n-3 LCPUFA in blood with increasing self-reported intake of fish and fish oil supplements. However, we cannot rule out any misclassification. Similar to all the exposure variables in paper I-IV, diabetes is self-reported in our study, and the prevalence in our population was lower than 2%. This is substantially less than the prevalence reported in western countries (about 10%) [208]. Hence, it is probably an underestimation of the true prevalence of diabetes. A similar underreport of alcohol consumption is possible to imagine. It has been shown that subjects tend to give more socially acceptable answers to the amount of alcohol they consume, often resulting in an underreport [209]. However, this kind of misclassification will probably be similar among those who experience a VTE and those who do not, and are thus non-differential. Also dietary patterns and physical activity may have been both under- and over reported, these misclassifications will accordingly be non-differential.
**Modifiable risk factors**

All of the exposure factors in paper I-IV are modifiable and may change over time. This is a potential limitation in prospective studies with long follow-up. During a follow-up time of 10-13 years, participants may have changed their drinking and dietary habits, and their level of physical activity. However, because these are random errors in measurements of a risk factor, it generally leads to an underestimation of the real association between the disease and the risk factors due to “regression dilution” [210]. Measuring exposure factors at baseline has been shown to underestimate the strength of the real association with one-third during the first decade [210]. This minimizes the possibility of finding false positive associations (type I errors), but enhances the risk of false negative associations (type II errors).

**Missing data**

Missing data is a problem that occurs in almost all studies. There are several reasons for missing data; (i) subjects do not complete the entire questionnaire, (ii) occasional data values for a variable are missing because of equipment failure, (iii) laboratory samples are lost in transit or technically unsatisfactory and (iv) other unknown reasons [211]. There are several methods for dealing with missing data. The main options are: (a) omitting variables which have many missing values, (b) omitting individuals who do not have complete data (complete-subjects analysis) and (c) replacing the missing values with a plausible value predicted from that individual’s available data (imputation) [211]. Complete subjects analysis is probably the most common method. However, it might yield problems with statistical power and, unless the data are missing completely by random, it could yield biased results.

In paper II we omitted about 13% of the population, mainly because they had not provided sufficient information about their dietary habits. However, the source population did not differ significantly from the study population. Factors like age, sex, BMI and incidence of
VTE were almost identical in the two populations. Thus, the chance of bias due deletion of those with missing data is reduced.

Detection and validation of outcome

All incident VTEs during the follow-up period were identified by retrospective search, through the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. The probability of a complete VTE-register is enhanced by the fact that the University Hospital of North Norway is the sole provider of health care in this region. However, one cannot rule out that some VTEs, diagnosed or treated outside of the region, were missed. In order to minimize the chance of outcome misclassification, the VTEs had to fulfill four solid criteria in order to be registered: (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral-computed tomography (CT), perfusion-ventilation scan, pulmonary angiography or autopsy); (ii) the medical record indicated that a physician had made a diagnosis of DVT or PE; (iii) signs and symptoms consistent with DVT or PE were present; (iv) therapy with anticoagulants (heparin, warfarin, or similar agent) thrombolytics, or vascular surgery were required. For subjects derived from the autopsy registry, a VTE-event was recorded as an outcome when the autopsy record indicated VTE as a cause of death or as a significant condition.

In spite of these solid methods and criteria, misclassification in registering VTEs cannot be ruled out. There may be insufficient information in the patients records used to detect the VTEs and to classify them as either provoked or unprovoked. The individual physician who examined the patients and recorded information about possible risk factors had no standard instructions to follow. However, the personnel registering the VTE-events were blinded to the baseline characteristics, so any misclassification would be non-differential.
Baseline information on previous history of VTE was unfortunately not available. Therefore subjects with prevalent VTE, who should have been excluded from the analysis, might have been included and treated as healthy participants. However, this would probably not affect the risk estimates significantly, because it would only yield small changes in the overall number of person-years at risk.

5.2 Discussion of main results

Alcohol consumption and VTE

Despite a generally low consumption of alcohol in their elderly female study population, Pahor et al. [154] found a 60% decreased risk of VTE for those consuming ≥1 Ounce (28.35 g) of alcohol per day, compared to non-consumers. A large Swedish cohort [155] including women aged 25-64 years, also found a reduced risk of VTE for those who had a moderate alcohol consumption (10 to <15 g/day) compared to non-consumers. The LITE-study [59] hypothesized that low alcohol consumption might increase the risk of VTE, but they found no such association. Similarly, Glynn et al. [1] found an inverse association between alcohol consumption and risk of CVD and stroke, but no association to VTE. Samama et al. [158] conducted a case-control study on risk factors for deep vein thrombosis in 1272 outpatients. They found no relationship between alcohol consumption and VTE. Contrary, a large Dutch study [157] including 4423 patients and 5235 controls, found that alcohol consumption was associated with reduced risk of VTE. The most pronounced beneficial effect (33% risk reduction) was found for those consuming 2-4 glasses per day.

Similar to our study, Lutsey et al. [156] aimed to assess both the impact of total alcohol consumption and different types of alcohol on the risk of VTE in the Iowa Women’s Health study. They found a 26% decreased risk of VTE for those consuming ≥7 glasses of alcohol per week, compared to non-consumers. This association was slightly attenuated after
adjustments for BMI and diabetes. In analyses of different alcohol types they found a significant decreased risk of VTE for beer only, but not for wine or liquor. In contrast, we found no association between total alcohol consumption and VTE risk, and only a weak association between beer consumption and the risk of VTE. However, we found a reduced risk of VTE for those consuming ≥ 3 units of wine per week. This is in accordance with several studies investigating the impact of alcohol on CVD, which concludes that wine have a superior antithrombotic effect compared to liquor and beer [212, 213]. Our finding is further supported by studies revealing several antithrombotic effects generated by resveratrol [214], a polyphenol found in the skin of grapes.

Contrary, we found a 53% higher risk of VTE for those consuming ≥ 3 units of liquor per week. A similar effect was found in those who were binge drinking more than once a week. These latter findings combined with the knowledge that binge drinking has been found to reverse the antithrombotic effect of moderate alcohol consumption [148, 215], raised the suspicion that the most frequent liquor drinkers and the most frequent binge drinkers might include some of the same subjects. Thus, we hypnotized that it was not the liquor itself, but the drinking pattern that yielded the increased risk of VTE in our analysis. In sub-analyses we revealed that 36% of those reporting binge drinking once or more per week were also among the most frequent liquor drinkers (corresponding numbers for wine and beer drinkers were 25% and 29%, respectively).

Further adjustments for the other alcohol types strengthened the relationships between beer, wine and liquor and VTE. The beneficial effect of wine and the harmful effect of liquor were increased, and the adjustments revealed that also beer consumption might be associated with a reduced risk of VTE. Furthermore, these findings indicate that the protective effect attributed to wine is not caused by absence of liquor and that the harmful effect of liquor is not due to the absence of wine.
Differences in study populations, and thereby differences in drinking habits, are probably the main explanation for the diverging results regarding the relationship between alcohol consumption and VTE. Some studies included only elderly women [154, 156], others only male physicians [1]. According to a report on drinking habits in England in 2007, drinking patterns differ significantly between men and women and young and elderly [216]. The same differences between gender and age-groups were found in a study conducted in Norway in the time period 1993-2000 [217]. Different cut-off values of alcohol consumption might be another explanation for the divergent results. IWHS [156] compared drinking one unit of beer, wine or liquor ≥1 time/week to drinking one unit <1 time/week. In paper I, we compared drinking ≥ 3 units/week with being a teetotaler, whereas the Dutch study [157] had ≥10 glasses per day as their highest exposure level.

A Japanese case-control study [218] investigated several risk factors for VTE, including alcohol consumption. Furthermore, three new studies were published in 2012, one case-control and two prospective cohort studies [140, 173, 219]. None of these four studies found any association between total alcohol consumption and the risk of VTE. Still, we need more studies investigating different types of alcoholic beverages and their impact on the risk of VTE in general populations.

**Diet and VTE**

There is substantial knowledge about the association between diet and the risk of arterial cardiovascular diseases [174, 220-222]. However, only few studies were published on the relationship between diet and VTE prior to the publication of paper II. In the LITE-study, Steffen et al. [171] found an inverse association between prudent dietary pattern and the risk of VTE, while a Western dietary pattern was associated with increased risk of VTE. Contrary, in the Iowa Women’s health study [156] no relationship between independent dietary factors
or dietary patterns and the risk of VTE was found. A Thai case-control study [172] investigated the association between dietary and behavioral factors and the risk of VTE. They found that VTE patients had a lower intake of vegetables compared to controls. In the Women’s Health Study [223] they investigated the association between adherence to a Dietary Approaches to Stop Hypertension (DASH) - style diet and the risk of cardiovascular disease and VTE. Both their design (investigating the association between diet and risk of CVD and VTE in the same population) and results were quite similar to our study. They found a borderline significant, moderate reduced risk of CVD for those with a healthy diet, but no association between healthy diet and risk of VTE. Another recently published cohort [173] investigated the relationship between diet and VTE in U.S. male health professionals and female nurses. They found no relation between a prudent pattern and the risk of VTE, and only a weak positive association between a western dietary pattern and VTE.

The results from the current studies on dietary habits and risk of VTE are diverging. There may be several possible explanations for this. First and foremost, the study populations differ significantly in both gender and age across the studies. Variances in ethnicity of the study populations may also be of importance. Studies have shown that cultural factors influence food-related behavior [224], and African- Americans have a higher incidence of VTE than White-Americans [39]. In addition, studies have shown a marked increase in the incidence of VTE in Asian patients [225, 226], and that the incidence is now comparable to Western countries [227]. An association between diet and VTE was found in the LITE study [171] where approximately 25% of the participants were African-American, and in the case-control study conducted in a Thai population [172]. Contrary, our study and the Women’s health study [223], in which no association between diet and VTE were found, constituted of predominantly white populations.
All studies run the risk of residual confounding and misclassification. We were able to show the known effect of a healthy diet on the risk of MI in our analysis, but found no association between diet and VTE. By conducting the analysis with both VTE and MI as endpoints in the same population, the risk of false negative findings caused by residual confounders or misclassifications is reduced. Lastly, the case-control study design, as is used in the Thai study, always runs the risk of recall bias.

*Fish consumption and VTE*

Only a few studies on fish consumption and risk of VTE are previously published. One found a protective effect of fish consumption [171], another found an increased risk [156], and finally two studies found no association between fish consumption and risk of VTE [172, 173].

In the LITE-study [171] they hypothesized that food rich in omega-3 fatty acids was inversely associated with VTE. They found a 30-45% reduced risk for those who consumed fish ≥1/week. Intake of omega-3 fatty acids as nutrients yielded similar result. The findings in the Iowa Women’s Health Study (IWH) [156] were quite different from the LITE study. In a multivariate model they actually found a 22% increased risk of VTE for women consuming fish ≥2 times/week, compared to those consuming fish <0.5 times/week. They did not investigate the relationship between omega-3 fatty acids as a nutrient and risk of VTE. Lutsey et al. [156] proposed that one explanation for these diverging findings could be very different study populations including different genders and age groups. For instance, studying dietary factors in elderly might be erroneous due to different metabolism and nutrient absorption. However, it should be considered that the high fish consumption among some participants in the IWH-study may possibly be due to health conditions, like cardiovascular diseases, which in turn could lead to a healthier diet (reverse causation). This possible confounder was not
adjusted for in the IWHS. The Thai case-control study [172] initially found an almost 3-fold increased risk of VTE associated with a low fish consumption. However, the association disappeared in multivariable analysis. Another prospective study [173] based on The Nurses’ Health study and Health Professionals Follow-up Study, found no association between fish consumption or omega-3 fatty acids and risk of VTE. However, including only nurses and other health professionals could result in impaired external generalizability.

We found that high fish consumption was associated with moderately reduced risk of VTE. When we stratified on use of fish oil supplements, we showed that those with a high fish intake who concurrently used fish oil supplements had substantially lower risk of VTE, whereas no association was found in those with a high fish consumption and no use of supplements. This may be explained by general characteristics and lifestyle habits in those with a high fish intake in our study, which are different from those of the typical fish eating population in other countries, who often are defined by their healthy lifestyle [178, 228]. Our high fish consuming population generally has a lower educational level, a lower intake of fruit and vegetables and a higher intake of saturated fat. They also have higher cholesterol and a higher proportion of diabetes and previous CVD. Conversely, those with a high intake of fish oil supplements in our population seem to be more similar to these ‘healthy lifestyle’-populations reported in other countries.

The validity of the information on fish consumption and intake of fish oil supplements extracted from a self-administered questionnaire can be questioned. However, we found a proportional increase of n-3 LCPUFA concentration in the blood with increasing self-reported fish consumption and intake of fish oil supplements, and expected lower levels of triglycerides for those with a higher intake of n-3 LCPUFA. Our results need to be confirmed, preferably by experimental studies investigating the effect of fish consumption on the risk of VTE.
Physical activity and VTE

A few studies published prior to paper IV found that physical activity was associated with reduced risk of VTE. One case-control study by Van Stralen et al. [190] found a 29% reduced risk of VTE for those performing sports regularly. Another case-control study [191] found a decreased risk of VTE for women using oral contraceptives who attended vigorous physical activity \( \geq 1 \) times/week compared to \( < 1 \) times/week. A study conducted in a cohort of Swedish women [155] also found strenuous exercise to reduce the risk of VTE compared to no exercise. However, the data about regular exercise were gathered retrospectively and may therefore be subjected to recall bias. Similar to our study, a prospective cohort investigating the relationship between exercise and risk of VTE in elderly [192] found a higher risk associated with high-intensity exercise. However, they also found a non-significant lower risk of VTE associated with low-intensity exercise. The Physicians’ Health Study [1] also found an increased risk of VTE associated with exercise, particularly for provoked events. Finally, the LITE-study [59] found no association between physical activity and risk of VTE. We found no effect of regular, moderate intensity physical exercise on the risk of VTE in a general population. In sub analysis however, we found that high amounts physical activity was associated with increased risk of provoked and total VTE in elderly and obese. Contrary, we found a decreased risk in subjects under 60 years and in subjects with a normal BMI (\(< 25 \text{ kg/m}^2\)) involved in moderate physical activity.

In 2011, an article based on the Nurses’ health study [229] was published. They found increased risk of PE due to physical inactivity, but no association between physical activity and PE. The Iowa Women’s Health Study [230], published the same year, initially found physical activity to be inversely associated with VTE, but the association was attenuated and became insignificant after adjustment for BMI. The same result was found [140] using data
from the Atherosclerosis Risk in Community study (ARIC). The initially inverse relationship between physical activity and VTE disappeared after adjustment for BMI.

In summary, except for the two case-control studies [190, 191] and the one prospective cohort [155], who collected the data on physical activity retrospectively, numerous prospective cohorts have failed to find a relationship between moderate physical activity and risk of VTE. This illustrates that different study designs might be one explanation for the diverging results. Some studies, counting paper IV included in this thesis, have found that strenuous physical activity increased the risk of VTE, predominantly in elderly. One can only speculate, but a plausible explanation may be that strenuous physical activity yields an increased risk of injuries [231] (especially in elderly), which in turn can lead to prolonged immobilization and a hypercoagulable state [232]. Other reasons for the diverging results may lie in the fact that the different studies have dissimilar study populations (only women, only men, only elderly etc.) and different methods for classifying physical exercise.
6. CONCLUSIONS

1) In our study we found reduced risk of VTE associated with increasing wine consumption, whereas liquor consumption and binge drinking was associated with an increased risk of VTE. Our findings raise the question of whether it is the ethanol itself or the drinking pattern that yields the increased risk of VTE in those consuming liquor, and if there are other constituents rather than ethanol in wine that are responsible for its possible favorable effect on the risk of VTE.

2) A heart healthy diet was associated with an expected reduced risk of MI. We found no association between diet and risk of VTE. Furthermore, the risk of MI was decreased in obese subjects consuming a heart healthy diet, while no such effect was found on the risk of VTE in obese.

3) We found that a high weekly intake of fish was associated with a moderately reduced risk of VTE. Addition of fish oil supplements strengthened the effect in those with a high fish consumption. Consumption of fatty fish was associated with a more pronounced reduced risk of VTE than lean fish consumption.

4) We found no significant association between regular, moderate physical activity and the risk of VTE in a general population. High amounts of physical activity did however yield an increased risk of provoked VTE and increased the risk of total VTE in elderly (>60 years) and obese (BMI>30 kg/m²), compared to inactive subjects. Contrary, moderate intensity physical activity was associated with a borderline significant decreased risk of VTE in younger subjects (<60 years) and subjects with BMI <25 kg/m², compared to inactive subjects.
7. REFERENCES


66. (WHO), T.W.H.O. *Chronic diseases and health promotion*.


Paper I
Paper II
Paper III
Paper IV
Appendix
Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø.
Tid og sted for frammøte finner du nedenfor. Du finner også en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber deg fylle ut spørreskjemaet på baksiden og ta det med til undersøkelsen.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

"GRIPSJANSEN - MØT FRAM!"
### EGEN HELSE

#### Hvordan er helsen din nå? *Sett bare ett kryss.*
- Dårlig .......................................................................................................................... 12
- Ikke høtt god ............................................................................................................. 2
- God ............................................................................................................................ 3
- Svært god .................................................................................................................. 4

<table>
<thead>
<tr>
<th>Har du, eller har du hatt:</th>
<th>Ja</th>
<th>Nei</th>
<th>Alder første gang</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjerteinfarkt..................</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (hjertekrampe)</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjemmeslag/hjerneslådning....</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astma ................................</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (sukkersyke) ........</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Bruker du medisin mot høyt blodtrykk?
- Nå ......................................................................................................................... 1
- Før, men ikke nå ................................................................................................... 2
- Aldri brukt ............................................................................................................ 3

<table>
<thead>
<tr>
<th>Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i musklar og ledd som har vært i minst 3 måneder sammenhengende?</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

#### Har du de siste to ukene følt deg:

<table>
<thead>
<tr>
<th>Nei</th>
<th>Litt</th>
<th>En god del</th>
<th>Svært mye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervøs eller urolig? .............................................</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaget av angst? ..................................................</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trygg og rolig? ....................................................</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritabel? ...........................................................</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glad og optimistisk? ............................................</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nedfør/deprimert? ................................................</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensom? ...............................................................</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MOSJON

#### Hvordan har din fysiske aktivitet i fritiden vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*
- Arbeidsverk regnes som fritid.  

<table>
<thead>
<tr>
<th>Timer pr. uke</th>
<th>Ingen</th>
<th>Under 1</th>
<th>1-2</th>
<th>3 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lett aktivitet (ikke svett/andepusen) .....................</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard fysisk aktivitet (svett/andepusen) ..................</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### KAFFE

#### Hvor mange kopper kaffe drinker du daglig?
- Sett 0 hvis du ikke dricker kaffe daglig.

<table>
<thead>
<tr>
<th>Antall kopper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kokekaffe</td>
</tr>
<tr>
<td>Annen kaffe</td>
</tr>
</tbody>
</table>

#### ALKOHOL

| Hvor mange ganger i måneden drinker du vanligvis alkohol? *Regn ikke med lettal.*
<table>
<thead>
<tr>
<th>Antall ganger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sett 0 hvis mindre enn 1 gang i måned.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hvor mange glass øl, vin eller brennevin drinker du vanligvis i løpet av to uker?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Øl</td>
</tr>
</tbody>
</table>

### FETT

#### Hva slags margarin eller smør bruker du vanligvis på brodet? *Sett et kryss.*
- Bruker ikke smør/margarin. ........................................... 71
- Meierismer ........................................................................ 72
- Hard margarin .................................................................... 73
- Bliet (soft) margarin ..................................................... 74
- Smer/margarin blanding .................................................. 75
- Lettmargarin ..................................................................... 76

### UTDANNING/ARBEID

#### Hvilken utdanning er den høyeste du har fullført?
- Grunnskole, 7-10 år, framhaldsskole, folkehøgskole .... 77
- Realskole, middelskole, yrkesskole, 1-2-årig videregående skole | 78
- Artium, øk.gymnas, allmennfaglig retning i videregående skole | 79
- Høgskole/universitet, mindre enn 4 år | 80
- Høgskole/universitet, 4 år eller mer | 81

### SYKDOM I FAMILIEN

<table>
<thead>
<tr>
<th>Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?</th>
<th>Ja</th>
<th>Nei</th>
<th>VET IKKE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>85</td>
</tr>
</tbody>
</table>
Helseundersøkelsen i Tromsø for dem som er 70 år og eldre.


Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komité for medisinsk forskningsetikett. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseredskaper etter de regler som Datatilsynet og Regional komité for medisinsk forskningsetikett gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø
Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du prøving.

Jeg ønsker ikke å besvare spørreskjemaet

Dag Mnd År

Dato for utlysning av skjema:

OPPVÆKST

I hvilken kommune bodde du da du fylte 1 år?

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

Meget gode
Gode
Vanskelige
Meget vanskellige

Hvor gamle ble dine foreldre?

Mor ble
Far ble

TIDLIGERE ARBEID OG ØKONOMI

Hvordan vil du beskrive det arbeidet du hadde de siste 5-10 årene før du ble pensjonert?

For det meste stillesittende arbeid?
(L.eks. skrivebordsarbeid, montering)
Arbeid som krever at du går mye?
(L.eks. ekspeditørarbeid, husmor, undervisning)
Arbeid hvor du går og løfter mye?
(L.eks. postbud, pieter, bygningsarbeid)
Tungt kroppsarbeid?
(L.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har du hatt noen av følgende yrker (heltdid eller dettid)?

Sett ett kryss for hvert spørsmål.

Ja Nei
Sjåfer
Bonde/gårdbruker
Fisker

Hvor gammel var du da du ble pensjonert?

Hva slags pensjon har du?

Minstensjon
Tilleggs Pensjon

Hvordan er din økonomi nå?

Meget god
God
Vanskelig
Meget vanskelig
HELSE OG SYKDOM

Er helsen din blitt ororandet det siste året?
Ja, dårligere ........................................................................62 □ 1
Nei, ufordret .........................................................................62 □ 2
Ja, bedre ...............................................................................62 □ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?
Mye dårligere ........................................................................62 □ 1
Litt dårligere ..........................................................................62 □ 2
Omtrent lik ..........................................................63 □ 3
Litt bedre ..............................................................................63 □ 4
Mye bedre .............................................................................63 □ 5

EGNE SYKDOMMER

Har du noen gang hatt: Søtt et kryss for hvert spørsmål. Oppgi alderen ved hendelsen.
Hvis det har skjedd flere ganger, hvor gammel var du siste gang?

Lårhilserbrudd ........................................................................64 □
Brudd ved håndledd/underarm .................................................67 □
Nakkesleng (whiplash) .............................................................70 □
Skade som følge av sykehusinleggselse .................................73 □
Sår på mage/kropp ....................................................................76 □
Sår på tolvingartermen .............................................................79 □
Magesår-operasjon ....................................................................82 □
Operasjon på halsen ...................................................................86 □

Har du eller har du hatt: Søtt ett kryss for hvert spørsmål.
Kreftsykdom ...........................................................................88 □
Epilepsi (falseske) .....................................................................88 □
Migrene ....................................................................................89 □
Parkinsons sykdom .....................................................................92 □
Kronisk bronkitt .......................................................................93 □
Psoriasis ....................................................................................93 □
Benskjæft (osteoporose) ..........................................................93 □
Fibromyalgi/sifos/krisk/smerter ..............................................93 □
Psykiske plager som du har søkt hjelp for .............................93 □
Stoffskiftesykdom (skjoldbrus/kjøtt) ......................................93 □
Sykdom i leveren .......................................................................96 □
Gjentatt, ufrivillig urinlekkasje .................................................96 □
Grøn stor ................................................................................96 □
Grå står ...................................................................................96 □
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Ledsgikt ................................................................................103 □
Nyreset ..........................................................104 □
Blindarmsoperasjon ...............................................................104 □
Allergi og overfølsomhet ........................................................106 □
Aloptisk eksem (f.eks. barneeksem) .........................................106 □
Håndeksem ............................................................................106 □
Høyterm ..........................................................106 □
Motvareallergi ..........................................................................106 □
Annen overfølsomhet (ikke allergi) ......................................106 □

Hvor mange ganger har du hatt forkjølelse, influensa, "røksjuka" og lignende siste halvår? 111 ganger

Har du hatt dette de siste 14 dager? ........................................113 □

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykmønene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

Mor Far Bror Søster Barn Ingen

Hjermeslag eller hjerneblødning ...........................................114 □
Hjerteinfarkt før 60 års alder .................................................120 □
Kreftsykdom ...............................................................................125 □
Høy blodtrykk ............................................................................125 □
Asthma .....................................................................................128 □
Benskjæft (osteoporose) ..........................................................134 □
Siltaesjegik (artrøse) .............................................................136 □
Psykiske plager ...........................................................................136 □
Alderdomssløvet ........................................................................138 □
Diabetes (sukkersyke) ..............................................................138 □
- alder da de fikk diabetes ......................................................138 □

Symptomer

Höster du omtrent daglig i perioder av året? .........................140 □
Hvis "Ja":
Hvis du har vanligvis ledet umiddelbart av oppsyyt? ..............140 □
Har du hatt slik hoste så lenge som noen vokser opp i en
3 måneders periode i begge de to siste årene? .......................140 □

Har du hatt episoder med piping i brystet? .........................141 □
Hvis "Ja", har dette oppstått:
Søtt et kryss for hvert spørsmål.
Om matten ..................................................................................141 □
Ved luftveisinfeksjoner .............................................................141 □
Ved fysiske anstrengelser .......................................................141 □
Ved sterk kulde ..........................................................................141 □

Har du merket anfall med plutselig endring
i pulsen eller hjertetrykken siste år? .................................142 □

Har du gått ned i vekt i siste året? .........................................143 □
Hvis "Ja":
Hvor mange kilo? ..............................................................143 □

Hvor ofte er du plagent av søvnløshet?
Aldri, eller noen få ganger i året ..............................................145 □
1-2 ganger i måneden .............................................................145 □
Omtrent en gang i uken ........................................................145 □
Mer enn en gang i uken ........................................................145 □

Hvis du er plagent av søvnløshet i perioder,
når på året er du mest plagent?
Ingen spesiell tid ..............................................................146 □
Sørlig i markedsføring ..........................................................146 □
Sørlig i midnatten .................................................................146 □
Sørlig når du sommerdager .................................................146 □

Pleier du å ta en kur på dagen? ..............................................146 □
Hvis du har vanligvis får nok søvn?
Ja Nei .........................................................................................146 □

Er du plagent av:
Svimmelhet ............................................................................148 □
Dårlig hukommelse ...............................................................148 □
Kraftløshet ...............................................................................148 □
Forstoppelse .............................................................................148 □

Litt I stor grad

Ja Nei □ □
### LEGEMILGE FUNSKJONER

<table>
<thead>
<tr>
<th>Klarer du selv disse gjermålene i det daglige uten hjelp fra andre?</th>
<th>Ja</th>
<th>Med noe hjelp</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gå innendørs i samme etasje</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gå i trappe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gå uten dør</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gå ca. 500 meter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gå på toalettet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaske deg på kroppen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bade eller dusje</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kje på og av deg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legge deg og stå opp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spise selv</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lage varm mat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gjøre lett husarbeid (f.eks. oppvask)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gjøre tyngre husarbeid (f.eks. gulvvaske)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gjøre inntjøp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta bussen</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vanskelig</th>
<th>Nei</th>
</tr>
</thead>
</table>

### BRUK AV HELSEVESNET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært: Antall ganger siste år

Seit 0 hvis du ikke har hatt slik kontakt.

- Hos vanlig lege/legevakt
- Hos psykolog eller psykiater
- Hos annen lege/psykiater utenfor sykehus
- På poliklinikk
- Innlagt i sykehus
- Hos fysioterapeut
- Hos kiropraktør
- Hos akupunktør
- Hos tannlege
- Hos fotterapeut
- Hos naturopat (homöopath, somatoterapeut, o.l.)
- Hos håndspåleger, synsk eller "leser"

### FAMILIE OG VENNER

<table>
<thead>
<tr>
<th>Har du nære familie som kan gi deg hjelp og støtte når du trenger det?</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis &quot;Ja&quot;; Hvem kan gi deg hjelp?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ektefelle/samboer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange gode venner har du som du kan snakke gode fortrolig med og gi deg hjelp når du trenger det? **297** venner

Tell ikke med dem du bor sammen med, men ta med andre slektninger!

Føler du at du har nok gode venner? **299**

Føler du at du hører med i et fellesskap (gruppe av mennesker) som stoler på hverandre og føler forpliktelse overfor hverandre (f.eks. i politisk parti, religiøs gruppe, slett, nasjonal, arbeidsplass eller organisasjon)?

- Sterk tilhørighet
- Normal tilhørighet
- Usikkert
- Liten eller ingen tilhørighet
### KOSTVANER

<table>
<thead>
<tr>
<th>Antall</th>
<th>Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)?</th>
<th>302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hvor mange ganger i uken spiser du varmmiddag?</td>
<td>.304</td>
</tr>
<tr>
<td></td>
<td>Hva slags type brød (kjapt eller hjemmebakt) spiser du vanligvis?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slett alt eller to kryss.</th>
<th>Loft</th>
<th>Fint brød</th>
<th>Kneip-brød</th>
<th>Grov-brød</th>
<th>Knekkebrød</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>306</td>
<td>310</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hva slags fett blir til vanligvis brukt til matlaging (ikke på brødet) i din husholdning?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meierismer</td>
</tr>
<tr>
<td>Hard margarin</td>
</tr>
<tr>
<td>Bløt (Soft) margarin</td>
</tr>
<tr>
<td>Smer/margarin blanding</td>
</tr>
<tr>
<td>Oljer</td>
</tr>
</tbody>
</table>

| Hvor mye i (antall glass, poteter eller brødskiver) spiser/drikker du vanligvis daglig av følgende matvarer? |

<table>
<thead>
<tr>
<th>Iningen</th>
<th>Mindre enn 1</th>
<th>1-2</th>
<th>3 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melk alle sorter (glass)</td>
<td>316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appelsinjuice (glass)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poteter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brødskiver totalt (inkl. knekkebrød)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brødskiver med</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- fiskepålegg (f.eks. makrell i tomat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- gulost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- kaviar</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### BESVARES BARE AV KVINNER

### MENSTRUASJON

<table>
<thead>
<tr>
<th>Hvor gammel var du da du fikk menstruasjon første gang?</th>
<th>336</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvor gammel var du da menstruasjonen sluttet?</td>
<td>338</td>
<td></td>
</tr>
</tbody>
</table>

### SVANGERSKAP

<table>
<thead>
<tr>
<th>Hvor mange barn har du født?</th>
<th>340</th>
<th></th>
</tr>
</thead>
</table>

I hvis du har født, tyyt ut for hvert barn barnets fødselsår og antall måneder du ammet barnet. Hvis du har født mer enn 6 barn, noter fødselsår og antall måneder med amming for dem nederst på siden.

<table>
<thead>
<tr>
<th>Barn:</th>
<th>Fødselsår:</th>
<th>Antall måneder med amming:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Har du i forbindelse med svangerskap hatt for høy bloedtrykk og/eller egghevite (protein) i urinen?

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>336</td>
</tr>
</tbody>
</table>

Hvis "Ja", i hvilket svangerskap?

<table>
<thead>
<tr>
<th>Svangerskap</th>
<th>Første</th>
<th>Senere</th>
</tr>
</thead>
<tbody>
<tr>
<td>For høy bloedtrykk</td>
<td>367</td>
<td></td>
</tr>
<tr>
<td>Egghvite i urinen</td>
<td>369</td>
<td></td>
</tr>
</tbody>
</table>

### ØSTROGEN-MEDISIN

Bruker du, eller har du brukt, østrogen-medisin?

<table>
<thead>
<tr>
<th>Tablett eller plaster</th>
<th>Nå</th>
<th>Før</th>
<th>Aldri</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>371</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krem eller stikkpiller</td>
<td>372</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvis du bruker østrogen, hvilket merke bruker du nå?

| Dine kommentarer: | 373 |
Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om kraftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse idelser. Vi ber deg derfor svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komité for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistrer etter de regler som Datatilsynet og Regional komité for medisinsk forskningsetikk gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø
Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du puffring.

Jeg ønsker ikke å besvare spørreskjemaet...

Dag Mnd År

Dato for uttylling av skjema: ...

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

Hvor mange av de første 3 årene av ditt liv bodde du i by?

Hvor mange av de første 15 årene av ditt liv bodde du i by?

Hvordan var de økonomiske forhold i familien under din oppvekst?

Oppvekst

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode...
- Gode...
- Vanskelige...
- Meget vanskelige...

Hvordan er boligen hovedsakelig oppvarmet?

- Elektrisk oppvarming...
- Vedfryzing...
- Sentralfrekvens oppvarming...
- Paraffin...
- Elektrisitet...

Oppvekst

- Er det heldekkende tepper i stua?
- Er det katt i boligen?
- Er det hund i boligen?

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?

For det meste stillsittende arbeid...
(f.eks. skrivebordsjobb, montering)
- Arbeid som krever at du går mye?
(f.eks. eksposeringsjobb, lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye?
(f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid?
(f.eks. skogsarb., tungt jordbruksarb., tungt bygningsarb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?

- Jeg, ikke i det hele tatt...
- I liten grad...
- Ja, i stor grad...
- Ja, det bestemmer jeg selv...

Hvor mange av de første 3 årene av ditt liv bodde du i by?
- Bodde du i by?
- Hadde dere katt eller hund i hjemmet?

Hvor mange av de første 15 årene av ditt liv bodde du i by?
- Bodde du i by?
- Hadde dere katt eller hund i hjemmet?

ARBEID

Oppvekst

- Hvor mange av barna har plass i barnehage?

- Hvor mange av barna er i barnehage?

- Hvor mange av barna har plass i barnehage?

- Hvor mange av barna er i barnehage?

- Hvor mange av barna har plass i barnehage?

- Hvor mange av barna er i barnehage?

- Hvor mange av barna har plass i barnehage?

- Hvor mange av barna er i barnehage?

- Hvor mange av barna har plass i barnehage?

- Hvor mange av barna er i barnehage?
### EGNE SYKDOMMER

<table>
<thead>
<tr>
<th>Har du noen gang hatt:</th>
<th>Ja</th>
<th>Nei</th>
<th>Alder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lårhalsbrudd</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brudd ved håndledd/underarm</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakkesleng (whiplash)</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skade</strong> som førte til sykehusinngjørelse</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sår på magesekken</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sår på tolvingertarmen</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magesår-operasjon</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operasjon på halsen</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sett et kryss for hvert spørsmål:**

<table>
<thead>
<tr>
<th>Har du eller har du hatt:</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsi (fallesyke)</strong></td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Migrøne</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kronisk bronkitt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benskjørt (osteoarose)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgi/fibrositt/kronisk smertesyndrom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psykiske plager som du har sakt hjelp for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stofskiftesyndrom (skjoldbruskkjertel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sykdom i leveren</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Nyrestein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindtarmsoperasjon</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Allergi og overfølsomhet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopisk eksem (f.eks. barneeksem)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Håndeksem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Høysynue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Møtvareallergi</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>Annen overfølsomhet (ikke allergi)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hvor mange ganger har du hatt forskjell, influensa, "ræksjuka" og lignende siste halvår?**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**Har du hatt dette siste 14 dager?**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

### SYMPTOMER

<table>
<thead>
<tr>
<th>Hoster du omtrent daglig i perioder av året?</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hvis &quot;Ja&quot;:</strong> Er hosten vanligvis ledsaget av oppsytt?</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td><strong>Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år?</strong></td>
<td>178</td>
<td></td>
</tr>
<tr>
<td><strong>Har du hatt episoder med piping i brystet?</strong></td>
<td>180</td>
<td></td>
</tr>
<tr>
<td><strong>Hvis &quot;Ja&quot;, har dette oppstått:</strong> Sett et kryss for hvert spørsmål.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Om natten</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Ved luftveisinfeksjoner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ved fysiske anstrengelser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ved sterk kulde</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år?**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>182</td>
<td></td>
</tr>
</tbody>
</table>

**Hvor ofte er du plaget av sovnløshet?**

| Aldri, eller noen få ganger i året | 184 |     |
| 1-2 ganger i måneden               | 185 |     |
| Omtrent en gang i uken             | 186 |     |
| Mer enn en gang i uken             | 187 |     |

**Hvis du er plaget av sovnløshet i perioder, når på året er du mest plaget?**

| Ingen spesiell tid                  | 188 |     |
| Særlig i mørketeiden                | 189 |     |
| Særlig i midnattsofjetiden          | 190 |     |
| Særlig vår og høst                   | 191 |     |

**Har du det siste året vært plaget av sovnløshet slik at det har gått ut over arbeidstiden?**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>192</td>
<td></td>
</tr>
</tbody>
</table>

**Hvor ofte er du plaget av hodepine?**

| Sjelden eller aldri                  | 193 |     |
| En eller flere ganger i måneden      | 194 |     |
| En eller flere ganger i uken         | 195 |     |
| Daglig                                 | 196 |     |

**Hender det at tanken på å få alvorlig sykdom bekyrmer deg?**

| Ikke i det hele tatt                 | 197 |     |
| Bare i liten grad                    | 198 |     |
| En del                                 | 199 |     |
| Ganske mye                            | 200 |     |

### SYKDOM I FAMILIEN

*Kryss av for de slektningene som har eller har hatt noen av sykdommene: Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.*

<table>
<thead>
<tr>
<th>Mor</th>
<th>Far</th>
<th>Bror</th>
<th>Søster</th>
<th>Barn</th>
<th>Ingen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hjemmelag eller hjerneblødding.**

| 113 |     |     |       |

**Hjerteintarkt før 60 års alder.**

| 110 |     |     |       |

**Kreftsykdom.**

| 112 |     |     |       |

**Asthma.**

| 113 |     |     |       |

**Mage/tolvfingertarm-sår.**

| 117 |     |     |       |

**Benskjørt (osteoarose).**

| 118 |     |     |       |

**Psykiske plager.**

| 119 |     |     |       |

**Allergi.**

| 120 |     |     |       |

**Diabetes (sukkeryke).**

| 121 |     |     |       |

- Alder da de fikk diabetes

| 122 |     |     |       |

### BRUK AV HELSEVESENET

**Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:**

<table>
<thead>
<tr>
<th>Slett 0 hvis du ikke har hatt slik kontakt.</th>
</tr>
</thead>
</table>

**Antall ganger siste år**

<table>
<thead>
<tr>
<th>Mor</th>
<th>Far</th>
<th>Bror</th>
<th>Søster</th>
<th>Barn</th>
<th>Ingen</th>
</tr>
</thead>
<tbody>
<tr>
<td>191</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hos vanlig legke/legevakt.**

| 192 |     |     |       |

**Hos psykolog eller psykiater.**

| 193 |     |     |       |

**Hos annen legesperesialist utenfor sykehus.**

| 194 |     |     |       |

**På poliklinikk.**

| 195 |     |     |       |

**Innlagt i sykehus.**

| 196 |     |     |       |

**Hos bedriftslege.**

| 197 |     |     |       |

**Hos fysioterapeut.**

| 198 |     |     |       |

**Hos kiropraktor.**

| 199 |     |     |       |

**Hos akupunktør.**

| 200 |     |     |       |

**Hos tannlege.**

| 201 |     |     |       |

**Hos naturmedisiner (homeopat, sonotherapeut o.l.).**

| 202 |     |     |       |

**Hos håndspålegger, psykisk eller "feser".**

| 203 |     |     |       |
**LEGEMIDLER OG KOSTTILSKUDD**


Legemidler

- Smertestillende ........................................... 215 mnd.
- Sovemedisin .................................................. 224 mnd.
- Beroigende midler ........................................... 227 mnd.
- Medisin mot depression ................................... 231 mnd.
- Allergiemedisin ............................................. 237 mnd.
- Astmamedisin ................................................ 234 mnd.

Kosttilskudd

- Jerntabletter .................................................. 227 mnd.
- Kalktabletter eller bennel ................................ 232 mnd.
- Vitamin D-tilskudd .......................................... 234 mnd.
- Andre vitamintilskudd ....................................... 233 mnd.
- Tran eller fiskeoljekapsler ................................ 234 mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?

*Sett ett kryss for hvert spørsmål.*

Legemidler

- Smertestillende medisin ..................................... 237
- Febersekende medisin ........................................ 238
- Migrenemedisin ............................................. 240
- Eksemsalve .................................................... 242
- Hjertemedisin (ikke blodtrykksmedisin) ................. 244
- Kolesterolsekende medisin ................................ 246
- Sovemedisin .................................................. 249
- Beroigende medisin ......................................... 251
- Medisin mot depression ..................................... 252
- Annen nervemedisin ......................................... 254
- Syromyraliserende midler .................................. 256
- Magesårsmedisin ............................................. 258
- Insulin ................................................................ 260
- Tabletter mot diabetes (sukkersyke) ...................... 262
- Tabletter mot lavt stoffskifte (thyroxin) ................. 264
- Kortisontabletter .............................................. 266
- Annen medisin ................................................ 268

Kosttilskudd

- Jerntabletter .................................................... 227 mnd.
- Kalktabletter eller bennel .................................. 232 mnd.
- Vitamin D-tilskudd ........................................... 234 mnd.
- Andre vitamintilskudd ....................................... 233 mnd.
- Tran eller fiskeoljekapsler ................................ 234 mnd.

**KOSTVANER**

Hvis du bruker smør eller margarin på brødet, hvor mange skiver rørreker en liten porspjanspakning vanligvis til? Vi tenker på slik porspjanspakning som du får på fry, på kafé o.l. (10-12 gram).

Den rørreker til omtrent ........................................... 265 skiver

Hva slags fett blir vanligvis brukt til matlaging (ikke på brødet) i din husholdning?

- Meierismør ...................................................... 266
- Hard margarin .................................................. 268
- Blød (Soft) margarin ........................................... 270
- Smør/margarin blanding ....................................... 272
- Øljer .................................................................. 274

Hva slags type brød (kjøpt eller hjemmebakt) spises du vanligvis?

*Sett ett eller to kryss!*

- Loff ................................................................. 275
- Fint brød ......................................................... 276
- Knæbøkbrød ...................................................... 277
- Grovbrød .......................................................... 278
- Knekkebrød ....................................................... 279

Bredtypen ligner mest på:

- 271
- 272

Hvor mye (i antall glass, kopper, poteter eller brødskiver) spiser eller drinner du vanligvis daglig av følgende matvarer?

*Kryst av for alle matvarane.*

- Færre .................................................................. 281
- Mer ..................................................................... 282

- Halmelk (søt eller sur) (glass) ......................... 273
- Lettmelk (søt eller sur) (glass) ......................... 274
- Skummet melk (søt eller sur) (glass) ................. 275
- Te (kopper) ....................................................... 276
- Appelsinjuice (glass) ......................................... 277
- Poteter ............................................................. 278
- Brødskiver totalt (inkl. knekkebrød) ................. 279

- Brødskiver med
  - fiskepålegg (t. eks. makrell i tomat) ................. 280
  - magert kjøtt (t. eks. skink) ......................... 281
  - fetere kjøtt pålegg (t. eks. salami) ............... 282
  - gulost ......................................................... 283
  - brunost ....................................................... 284
  - kaviar ......................................................... 285
  - syltetøy og annet satt pålegg ....................... 286

Hvor mange garner i uka spiser du vanligvis følgende matvarer?

*Kryst av for alle matvarene.*

- Yoghurt ........................................................... 287
- Kokt eller stekt egg ......................................... 288
- Frokostblanding/havregryn o.l. ......................... 289

**VENNER**

Hvor mange gode venner har du som du kan snakke gode fortrolig med og gi deg hjelp når du trenger det? .... 259 venner

Tall ikke med de du bor sammen med, men ta med andre slektnings!

Hvor mange av disse gode vennene har du kontakt med minst en gang i måneden? .. 261

Føler du at du har nok gode venner? 263

Hvor ofte tar du vanligvis del i foreningsvirksomhet som t. eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året .......................... 264
- 1-2 ganger i månedene ...................................... 265
- Omtrent en gang i uken ..................................... 266
- Mer enn en gang i uken .................................... 267
**ALKOHOL**

<table>
<thead>
<tr>
<th>Hvor ofte pleier du å drikke</th>
<th>øl?</th>
<th>vin?</th>
<th>brennevin?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldri</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 ganger i måneden</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omtrent 1 gang i uken</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3 ganger i uken</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omtrent hver dag</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Omtrent hvor ofte har du i løpet av siste år drukket alkohol tilsvarende minst 5 halvflasker øl, en helflaske vin eller 1/4 flaske brennevin? [ ]

<table>
<thead>
<tr>
<th>Ikke siste år</th>
<th>311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noen få ganger</td>
<td>2</td>
</tr>
<tr>
<td>1 - 2 ganger per måned</td>
<td>3</td>
</tr>
<tr>
<td>1 - 2 ganger i uken</td>
<td>4</td>
</tr>
<tr>
<td>3 eller flere ganger i uken</td>
<td>5</td>
</tr>
</tbody>
</table>

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? [ ]

312 år

**SLANKING**

Omtrent hvor mange ganger har du bevisst prøvd å slanke deg? Sætt 0 hvis ingen forsøk.

- før 20 år [ ]
- senere [ ]

Hvis du har slanket deg, omtrent hvor mange kilo har du på det meste gått ned i vekt?

- før 20 år [ ]
- senere [ ]

Hvilken vekt ville du være tilfreds med (din 'trivselsvekt')?

- før 20 år [ ]
- senere [ ]

**UFRIVILLIG URINLEKKASJE**

Hvor ofte har du ufriivillig urinlekkasje?

<table>
<thead>
<tr>
<th>Aldri</th>
<th>325</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikke mer enn en gang i måneden</td>
<td>2</td>
</tr>
<tr>
<td>To eller flere ganger i måneden</td>
<td>3</td>
</tr>
<tr>
<td>Ukeentlig eller ofttere</td>
<td>4</td>
</tr>
</tbody>
</table>

Dine kommentarer:

**BESVARES BARE AV KVINNEN**

**MENSTRUASJON**

Hvor gammel var du da du fikk menstruasjon første gang? [ ]

326 år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? [ ]

328 år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blodningsfri i minst 6 måneder? [ ]

Ja [ ]

Nei [ ]

Hvis 'Ja', hvor mange ganger? [ ]

331 ganger

Hvis du fremdeles har menstruasjon eller er gravid: [ ]

dag/ mnd/ år

Hvilken dato startet din siste menstruasjon? [ ]

333 / /

Bruker du vanligvis smertestillede legemidler for å dempe menstruasjonsplager? [ ]

Ja [ ]

Nei [ ]

**SVANGERSKAP**

Hvor mange barn har du født? [ ]

340 barn

Er du gravid nå? [ ]

Ja [ ]

Nei [ ]

Usikker [ ]

Har du i forbindelse med svangerskap hatt for høy blodtrykk og/eller egggevite (protein) i urinen? [ ]

Ja [ ]

Nei [ ]

Hvis 'Ja', i hvilket svangerskap? [ ]

Svangerskap Forste Senere

For høy blodtrykk [ ]

Egggevite i urinen [ ]

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.

<table>
<thead>
<tr>
<th>Barn:</th>
<th>Fødselsår:</th>
<th>Antall måneder med amming:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>348</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>356</td>
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</tr>
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<td></td>
<td></td>
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<tr>
<td>5</td>
<td>364</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PREVENSJON OG ßOSTROGEN**

Bruker du, eller har du brukt:

- P-pille (også minipille) [ ]
- Hormonspiral [ ]
- ßestrogen (tablett eller plaster) [ ]
- ßestrogen (krem eller stikkpiller) [ ]

Hvis du bruker P-pille, hormonspiral eller ßestrogen; hvilket merke bruker du nå? [ ]

372

Hvis du bruker eller har brukt P-pille:

Aldri da du begynte med P-piller? [ ]

396 år

Hvor mange år har du tilsammen brukt P-pillere? [ ]

382 år

Dersom du har født, hvor mange år brukte du P-pillere før første fødsel? [ ]

384 år

Hvis du har sluttet å bruke P-pillere:

Aldri da du sluttet? [ ]

396 år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsene i Tromsø