CARDIOVASCULAR RISK FACTORS AND RISK OF VENOUS THROMBOEMBOLISM

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LIST OF PAPERS

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ABBREVIATIONS

ADP: Adenosine diphosphate

APC: Activated protein C

BMI: Body mass index

CAD: Coronary artery disease

CHD: Coronary heart disease

CI: Confidence interval

CRP: C-reactive protein

CVD: Cardiovascular disease

DVT: Deep vein thrombosis

HbA1c: Glycosylated haemoglobin

HDL: High density lipoprotein

HR: Hazard ratio

hs-CRP: high sensitivity C-reactive protein

ICD: International classification of diseases

LDL: Low density lipoprotein

LITE-study: Longitudinal Investigation of Thromboembolism Etiology-study

Lp (a): Lipoprotein a

MI: Myocardial infarction

MPV: Mean platelet volume

NCEP-ATPIII: National Cholesterol Education Programme - Adult Treatment Panel III

PAI-1: Plasminogen activator inhibitor 1

PE: Pulmonary embolism

RCT: Randomized controlled trial

VTE: Venous thromboembolism

vWF: von Willebrand factor

1. INTRODUCTION

1.1 Venous thromboembolism

Deep vein thrombosis (DVT) is the formation of a blood cloth in the deep veins. DVT usually affects the large veins of the leg or thigh, but can also occur in other parts of the body. Pulmonary embolism (PE) occurs when a blood clot dislodges from its original site and embolize to the arterial blood supply of the lungs. DVT and PE are collectively referred to as venous thromboembolism (VTE). VTE is a relatively common disorder that affects 1-2 per 1000 individuals each year, and the incidence increases markedly with age, from about 1 per 10 000 in young adults, to 1 per 100 in elderly [1]. In most studies, the incidence of clinically diagnosed DVT is reported to be approximately twice that of PE [2]. However, DVT and PE share the same underlying pathology and the two conditions are often presented at the same time. Among subjects with acute DVT, concurrent, clinically silent PE is found in 30-50 % [3]. Likewise, among those with acute PE, clinically silent DVT is present in about 80 % of the subjects [4].

VTE is the third most common life-threatening cardiovascular disease [5], and is a major cause of morbidity and mortality. The one-week survival rate after a PE is approximately 70 %, and almost 25 % of all PE-cases essentially present as sudden death [6]. VTE is associated with short term complications such as local extension of the disease, further embolization and recurrence of the disease within weeks to months of the initial episode. Serious long-term complications includes the post-thrombotic syndrome, venous insufficiency, pulmonary hypertension and late risk of recurrent VTE [4,7].

In 1859, the brilliant pathologist Rudolph Virchow concluded that (i) blood stasis, (ii) hypercoagulability and (iii) changes in the vessel wall were the major factors responsible for the development of VTE [8]. The triad still applies, and if one examines the commonly accepted risk factors for VTE, nearly all fall into one or more of these categories. Today, VTE

is recognized as a complex, multifactor disease involving both environmental exposures as well as genetic and environmental interactions. Acquired risk factors include advancing age, obesity, surgery, trauma, hospitalization, acute medical conditions, malignancy, immobilization, pregnancy, use of estrogens and the lupus anticoagulant [9,10]. Inherited thrombophilic factors that predispose to VTE include factor V Leiden mutation, prothrombin 20210A mutation, elevated levels of factor VIII, activated protein C (APC) resistance and deficiencies of antithrombin, protein C or protein S [9].

Advanced age is a well-accepted, independent risk factor for VTE [1]. The Longitudinal Investigation of Thromboembolism Etiology (LITE) study found that age independently increased the risk of VTE by approximately 2-fold per decade, and that subjects older than 75 years had a 15-fold increased risk compared to those aged 45-54 years [11]. In patients hospitalized for VTE there was an exponential relationship between VTE incidence and age, with a 2-fold increase per decade [12]. Although it is not certain why risk is dependent on age, it has been suggested that it might be related to a combination of factors such as decreased mobility and degenerative vascular changes [13].

During the recent years, growing evidence for obesity as a risk factor for VTE has been presented. Data from the Physicians' Health Study [5] indicated that BMI is a strong predictor for VTE. Furthermore, BMI $\geq$ 30 kg/m^2 was associated with a 2 to 3-fold increased risk of VTE [11] and PE [14] in prospective studies. A prospective study among middle-aged men identified waist circumference as an independent predictor for VTE [15], and increased waist circumference and waist hip ratio have been reported in case-control studies among patients with unprovoked VTE [16] and recurrent VTE [17].

Previous studies have reported that hospitalized patients have substantially increased risk of VTE compared to non-hospitalized patients [10,18]. Furthermore, PE accounts for approximately 10 % of all in-hospital deaths [19]. Major surgery is a well recognized risk

factor for VTE, and surgery within the last 45-90 days confers a 4-22 fold increased risk of VTE [20]. Active malignant disease has been shown to be an independent risk factor for VTE [10,21], and the incidence of VTE in cancer populations has been reported to be 5-fold higher than that of the general population [22]. Overall, 18–29% of all VTE events in the community have been shown to be associated with cancer [23-25]. Several other clinical conditions are associated with increased risk of VTE. The incidence of subclinical DVT in patients hospitalized with acute medical conditions such as acute MI, stroke, heart failure and acute infections varies from 20-50 % [26,27].

Compared to non-pregnant subjects the risk of VTE is estimated to be 4 to 5-fold increased during pregnancy [28,29], and approximately 20-fold increased postpartum [28]. Fatal PE remains the most common cause of maternal mortality in many western countries [30]. Estrogen therapy, such as oral contraceptives and hormone replacement therapy, is also associated with increased risk of VTE. The absolute risk of VTE is 2 to 4-fold higher in women taking second-generation oral contraceptives, and 3 to 8-fold higher in women taking third-generation oral contraceptives [31]. In a meta-analysis of 12 studies the relative risk of VTE was 2.1 among current users of hormone replacement therapy, and the risk was highest (RR=3.5) during the first year of use [32].

Inherited thrombophilia is a genetically determined tendency to form thrombosis. The most common prothrombotic abnormalities include APC resistance (e.g. factor V Leiden mutation), prothrombin G20210A mutation, deficiencies of antithrombin, protein C or protein S and elevated levels of factors VIII, IX and XI [33]. APC resistance is caused by a single point mutation in the factor V gene which leads to inefficient cleavage of factor V. The mutation is present in 3-5 % of the Caucasian population, and is associated with a 7-fold increased risk of DVT in heterozygous individuals [34] and 80-fold increased risk in homozygous individuals [35]. Thrombin, the activated form of prothrombin, plays a key role

in the conversion of fibrinogen to fibrin and platelet activation. The overall prevalence of the prothrombin G20210A mutation, a one nucleotide change in the prothrombin gene, is about 2 % in the healthy European population [36]. The mutation is associated with an approximately 3-fold increased risk of VTE [37], dependent on the presence of additional inherited or acquired risk factors [38]. Antithrombin deficiency is a rare genetic defect found in 1-2 % of VTE patients, and is associated with a 10 to 20-fold increased risk of VTE [39,40]. Heterozygous deficiency of protein C is present in 2-5 % of VTE patients and 0.3-0.5 % of healthy controls, suggesting a 10-fold increased risk of VTE [40]. The prevalence of protein S deficiency in the general population is unacquainted [41], but family studies have suggested that the risk of VTE is similar to that in patients with protein C deficiency or APC-resistance [41-43].

Despite the identification of several inherited and acquired risk factors associated with VTE, still 30-50 % of the VTE-cases are unprovoked, i.e. they occur in the absence of obvious predisposing factors [2,44]. Clearly, there are still unrecognized environmental and/or genetic risk factors for VTE. Consequently, identification of new risk factors is essential in order to enhance the understanding of pathophysiological mechanisms of VTE, and to optimize individual risk stratification and treatment of the disease.

1.2 Possible link between arterial and venous thrombosis

Traditionally, arterial thromboembolic disease (acute myocardial infarction (MI), stroke and peripheral artery disease) and VTE has been considered as separate diseases, with different pathology, epidemiology and treatments. Platelet-fibrin haemostatic plugs are the pathophysiological basis for both arterial and venous thrombosis, but the different clinical presentations of the diseases, and the obvious anatomical differences in the composition of the

thrombi, have contributed to the concept of these conditions as distinct entities. Arterial cardiovascular disease is mainly associated with atherosclerosis. Arterial thrombi tend to occur at atherosclerotic plaque lesions, where share rates are high, and are platelet rich 'white thrombi'. In contrast, thrombi that form in the slow-flowing venous system are rich in red cells and fibrin, and are referred to as 'red thrombi'. Compared to the detailed knowledge of arterial thrombosis, where mechanisms are well understood even to the molecular level, our current understanding of the pathophysiological mechanisms of VTE is limited. However, development of venous thrombi has traditionally been thought to arise from reduced blood flow and states of hypercoagulability rather than atherosclerosis.

Recently, the concept of this clear-cut distinction between arterial and venous thrombosis has been challenged. In 2003, Prandoni et al. reported a higher frequency of carotid plaques in patients with unprovoked DVT compared to hospitalized controls [45]. This study certainly re-opened the case of a potential link between arterial and venous thrombosis. However, later prospective studies have shown diverging results regarding subclinical atherosclerosis and VTE. A significant relation between carotid intima media thickness and VTE was found in a prospective cohort of 13 081 middle-aged subjects, but the association disappeared when adjusting for atherosclerotic risk factors [46]. Another study in elderly subjects failed to show any association between subclinical atherosclerosis and VTE [47]. Studies of the association between arterial thromboembolic disease and VTE showed that subjects with VTE had increased risk of arterial events compared to the general population [48,49], and that the risk of arterial events was higher in subjects with unprovoked VTE compared to subjects with provoked VTE [50,51]. Another study showed that a first arterial event was associated with subsequent development of VTE [46]. Recently, a large Danish cohort study reported that the long-term incidence of cardiovascular disease was substantially increased in patients with VTE compared to population controls [52]. However, the latter

study did not investigate potential common risk factors, and thus adjustments could not be made for factors such as BMI and other arterial cardiovascular risk factors.

In summary, increasing evidence supports the concept of a link between arterial and venous thrombosis. However, the studies show somewhat diverging results. In addition, some of the studies have considerable methodological limitations, as most of the studies were carried out in specific populations such as middle-aged [46] or elderly [47], and the majority used hospitalized controls rather than healthy subjects [45,50,51]. Thus, further research, preferably prospective, population-based studies, are required to establish the magnitude and possible causes of an association between arterial thromboembolic disease and VTE. It is also important to consider the associations of VTE with three stages of the development of arterial cardiovascular disease; that is risk factors, subclinical disease, and clinical disease.

1.3 Cardiovascular risk factors and risk of venous thromboembolism

In 2006, Angelli and Becattini [53] stated that 'the sharing of common risk factors would certainly reinforce the link between atherosclerosis and VTE and could lead to the view that arterial and venous thrombosis are different presentations of the same disease'. A recent meta-analysis, based on mainly case-control studies and selected prospective studies with verified endpoints, concluded that cardiovascular risk factors such as obesity, hypertension, diabetes mellitus and low HDL-cholesterol were significantly associated with VTE [54]. However, prospective studies on relation between traditional cardiovascular risk factors and VTE show diverging results. In the Nurses' Health Study, a prospective cohort of 112 822 female nurses aged 30-55, obesity, cigarette smoking and hypertension, but not diabetes or elevated cholesterol, were independent predictors for PE [14]. In the Physicians' Health Study [5], a prospective cohort of 18 622 male physicians followed for over 20 years, only BMI and

height were identified as independent risk factors for VTE, whereas smoking and abdominal obesity were predictors for VTE in another study on 855 Swedish middle-aged men [15]. In the LITE-study, a prospective cohort of 19 293 men and women aged 45 or older, obesity and diabetes, but not cigarette smoking, hypertension and dyslipidemia, showed independent association to VTE [11]. In the Copenhagen City Heart Study, investigating 9 238 men and women, total cholesterol, HDL-cholesterol (inverse), diabetes and smoking were associated with VTE [55] in crude analysis, but further adjustments for potential confounders such as age, gender or BMI were not undertaken, nor were the results presented in multivariable analysis.

The observed inconsistency between these studies may to some extent rely on differences in study design, presentation of data, outcome verification and study population. In general, the results of case-control studies are affected by the selection of cases, eligible control group and to what extent the disease state and other confounders affect the predictor variable. Some of the prospective studies presented crude data only [55], while others had made adjustments for various potential confounders [11]. Outcome detection and verification differed as some of the studies relied on self-reported outcome [5,11,14] whereas others had objectively detected VTE-events [55]. In addition, several studies were performed in highly selected population groups such as female nurses [14], male physicians [5] middle-aged men [56] and postmenopausal women [57]. Thus, to establish the true associations between various cardiovascular risk factors and VTE, these hypotheses should be further investigated in large, prospective, cohort studies of general populations, preferably with objectively detected and validated outcome measures.

1.4 Metabolic syndrome and risk of venous thromboembolism

The metabolic syndrome is a cluster of cardiovascular risk factors [58]. According to guidelines from the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) the presence of 3 of 5 factors is required to establish the diagnosis [59]. These factors include insulin resistance, abdominal obesity, high triglyceride levels, low HDL-cholesterol levels and hypertension [59]. Although the prevalence of the components of the metabolic syndrome is increased in obesity [60], it is important to notice that not all obese subjects develop the metabolic syndrome, and even non-obese individuals can carry the syndrome.

The metabolic syndrome is a cluster of interrelated risk factors of metabolic origin, that appear to directly promote the development of atherosclerotic cardiovascular disease and diabetes mellitus [59,61]. Epidemiological studies have shown that the metabolic syndrome is associated with increased risk of coronary heart disease (CHD), cardiovascular disease (CVD), and overall mortality [62,63]. Several factors contribute to cause a hypercoagulable state in patients with the metabolic syndrome. Adipose tissue is a remarkable endocrine organ that produces prothrombotic and inflammatory molecules [64], and fibrinolytic activity and function are impaired in subjects with the metabolic syndrome, mainly related to visceral obesity and insulin resistance [65,66]. Individuals with the metabolic syndrome exhibit increased plasma levels of plasminogen activator inhibitor-1 (PAI-1) [67], and clotting factors VII and XIII [68]. Subjects with the metabolic syndrome usually exhibit a higher platelet activity than those with conventional risk factors for vascular disease [69]. Hyperinsulinemia and dyslipidemia have been associated with induction of endothelial dysfunction, and endothelial dysfunction, measured by flow mediated dilation to assess nitric oxide bioavailability, is commonly found in subjects with the metabolic syndrome [68]. Altogether,

these prothrombotic factors associated with the metabolic syndrome contribute to potentially increase the risk of future thrombotic events in both the arterial and venous system.

An intriguing question to investigate is whether the metabolic syndrome, as well as its predefined individual components, is associated with VTE. To date, only a few studies have investigated this relationship. Two recent case-control studies demonstrated a two-fold higher prevalence of the metabolic syndrome in patients with unprovoked DVT [16] and recurrent VTE [17] compared to controls, whereas a prospective study of 5 522 adults with CVD or diabetes [70] failed to show an association between the metabolic syndrome and VTE, but found a higher incidence rate of VTE in patients with abdominal obesity. Differences in study design, eligible control groups and definitions of the metabolic syndrome could be a possible explanation for the observed inconsistency between these studies. Thus, the relationship between the metabolic syndrome and VTE should be further examined in large cohort studies.

1.5 HDL-cholesterol and risk of venous thromboembolism

Atherosclerosis is a chronic, progressive disease which involves the formation of lesions in the arteries mainly characterized by accumulation of lipids, inflammation, cell death and fibrosis [71]. An atherosclerotic plaque contains inflammatory and immune cells, lipids, extracellular matrix, vascular smooth muscle cells and acellular lipid-rich debris [72]. The atherosclerotic lesions typically present as asymmetric thickening of the innermost layer of the artery (intima), a process that begins with the formation of fatty streaks which can progress into mature atherosclerotic plaques (atheromas). An atheroma typically comprises a core of extracellular lipid droplets and foam cells surrounded by a cap of smooth muscle cells and collagen-rich matrix [73]. With time, the plaque can progress into a more fibrotic and complex lesion which eventually leads to clinical manifestation of CAD or other

atherosclerotic disease. A rupture or fissuring of the fibrous cap displays the prothrombotic material in the lesion to the blood stream, and this may trigger an acute fatal thrombosis. The risk of clinical events is associated with plaque morphology [74]. Lipid rich, soft plaques covered by a thin fibrotic cap are more prone to rupture and cause clinical events compared to collagen-rich, hard plaques [74].

The protective effect of high density lipoprotein (HDL) cholesterol against CAD was first identified in the Tromsø Study more than three decades ago [75], and consistent findings in subsequent epidemiological studies have established low HDL-cholesterol as a strong risk factor for CAD [76,77]. HDL-cholesterol is thought to protect against CAD through both antiatherogenic and antithrombotic mechanisms. HDL-mediated transport of excess cholesterol from peripheral tissue is considered to be the main antiatherogenic function of HDL-cholesterol [78]. In addition, several other properties are likely to contribute to the atheroprotective action of HDL. Low density lipoprotein (LDL) oxidation is commonly considered a key factor in the initiation and progression of atherosclerosis [79]. HDL-cholesterol protects both lipid and protein moieties of LDL from oxidation via several mechanisms [80-82]. HDL exerts anti-inflammatory properties by its ability to decrease the expression of adhesion molecules to endothelial cells and inhibit monocyte adhesion to the endothelium [83,84], and HDL also improves endothelial function by mechanisms such as stimulation of nitric oxide synthesis [85-87], inhibition of the vasoconstrictor endothelin-1, and stimulation of endothelial cell migration and survival [88,89]. Furthermore, HDL exerts several antithrombotic properties. HDL improves blood flow by increasing nitric oxide and prostaglandin I_2 production [88]. HDL downregulates E-selectin and tissue factor [88], and promotes fibrinolysis by downregulating plasminogen activator inhibitor 1 (PAI-1) and upregulating tissue plasminogen activator [90]. Moreover, HDL attenuates platelet activation and aggregation [91-93], and activates the endogenous anticoagulants protein C and S [94]. In

epidemiological studies, HDL-cholesterol has been associated with increased plaque echogenicity, suggesting that high levels of HDL-cholesterol provide more stable plaques [95]. High levels of HDL-cholesterol has also been shown to reduce plaque growth in subjects with pre-existing carotid atherosclerosis [96].

Several studies have suggested that high HDL-cholesterol is associated with decreased risk of venous thrombosis and have posed the concept that HDL-cholesterol protect against VTE [55-57,97-99]. Recently, a meta-analysis, including mostly case-control studies, concluded that low HDL-cholesterol predispose to VTE [54]. This interpretation is supported by the antiatherogenic and antithrombotic properties of HDL particles [88,100]. However, data from large cohort studies, not included in the meta-analysis due to methodological considerations, showed no association between HDL-cholesterol and VTE [5,14]. Furthermore, original data from the LITE-study showed no association between HDL-cholesterol and VTE [11], and a recent publication presenting a more extensive examination of HDL-cholesterol, including a nested case-control subset of Apo-I and HDL fractions, did not reveal any association with VTE in the LITE-study [101].

1.6 Platelet function and risk of venous thromboembolism

The hemostatic system is simultaneously able to maintain the blood in a fluid state, so that it can circulate, and to convert the blood into an insoluble gel at sites of vascular injury. The hemostatic system is based on a complex interplay between platelets and coagulation proteins [102]. Platelets play a key role in the initiation of a blood clot. In response to vascular damage, platelets adhere to the vascular subendothelium via von Willebrand factor (vWF) bridging between subendothelial macromolecules and glycoprotein Ib receptors on the platelet surface [103]. Secretion of mediators including adenosine diphosphate (ADP), thrombin,

epinephrine and thromboxane A_2 amplify and sustain the initial platelet response, and recruit circulating platelets to form a growing hemostatic plug [104]. Transmembrane signalling by ligated receptors activates the platelets and induces α-granule release with the secretion of various procoagulant molecules such as factor V, vWF and fibrinogen. Activated platelets undergo a flip-flop reaction exposing phosphatidylserine to the outer membrane leaflet. The phospholipids provide a surface for the assembly of coagulant enzyme complexes which generate thrombin and enable fibrin deposition, stabilizing the clot.

It is well recognized that platelets play an important role in the pathophysiological development of atherothrombosis [104]. Recent evidence also suggest that platelets contribute to the progress of atherosclerotic lesions by numerous inflammatory properties [104]. In acute atherothrombosis, platelets rapidly adhere to the site of plaque disruption and initiate the coagulation process, resulting in thrombus formation [74]. The sequence of events leading to venous thrombi is less clear. Venous and arterial thrombi differ in composition, as arterial thrombi predominantly consist of platelets and a small amount of fibrin and red cells, while venous thrombi predominantly consist of red cells and fibrin. Based on the histopathologic structure of venous thrombi, platelet aggregation has traditionally not been considered an important pathophysiological mechanism of thrombus formation within the venous system. However, experimentally induced venous thrombus in the presence of radiolabeled platelets shows early accumulation of platelets at the head of the thrombus [105]. Moreover, antiplatelet agents have been shown to be effective for prevention of venous thromboembolic disorders, although to a smaller extent than anticoagulants [106,107].

The impact of platelet function and platelet count on the risk of VTE has not been extensively examined in prospective studies. Only a few studies have investigated the relationship between platelet count and VTE. In the LITE-study [11], a prospective study of 19 293 men and women followed for a mean of 7.8 years, elevated platelet count was not

associated with increased risk of VTE. Likewise, a prospective follow-up study of 5 766 elderly showed no association between platelet count and VTE [108]. Furthermore, limited data exists on the relationship between platelet function and VTE. Recently, increased levels of P-selectin, a marker of platelet activation, have been shown in VTE patients [109], and higher circulating P-selectin was associated with increased risk of recurrent VTE in patients with first unprovoked VTE [110].

Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function. Increased platelet volume is correlated with increased platelet reactivity [111], shortened bleeding time [111] and increased platelet aggregation ex vivo [112]. Large platelets have a higher thrombotic potential than small platelets [113], and express higher levels of platelet activation markers, such as P-selectin [114]. Studies have shown increased levels of MPV in patients with CAD [115,116], and MPV has been identified as an independent risk factor for MI and stroke [117-119]. To date, no study has investigated a possible relationship between platelet function, measured as MPV, and risk of VTE.

2. AIMS OF THE STUDY

The aims of the study were:

- To investigate the impact of traditional cardiovascular risk factors on the risk of venous thromboembolism in a prospective, population-based cohort-study.

- To examine the association between the metabolic syndrome and its individual components on the future risk of venous thromboembolism.

- To investigate the impact of HDL-cholesterol on the incidence of venous thromboembolism.

- To investigate the impact of MPV and platelet count on the risk of venous thromboembolism.

3. STUDY POPULATION AND METHODS

3.1 The Tromsø Study

The Tromsø Study is a single centre longitudinal population study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway. The study is conducted by the Institute of Community Medicine at the University of Tromsø, and the main focus is on cardiovascular disease. The first survey was carried out in 1974, followed by surveys in 1986-87, 1994-95, 2000-01, and 2007-08.

The fourth survey of the Tromsø Study (Tromsø IV) was conducted in 1994-95 and comprised two screening visits with an interval of 4-12 weeks. All inhabitants aged > 24 years were invited to the first screening visit, and a total of 27 158 subjects participated (77 % of the eligible population). All participants aged 55 to 74 years and 5-10% samples in the other 5-year birth cohorts (25-54 years and ≥ 75 years) were invited to a more extensive second visit, and a total of 6 889 subjects participated (78 % of the eligible population).

The four papers included in this thesis are all based on a prospective follow-up study on subjects who participated in Tromsø IV. Participants were followed from the date of enrolment in 1994-95 through September 1, 2007, and all first lifetime events of VTE during this 14-year study-period were recorded.

3.2 Baseline measurements - cardiovascular risk factors (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-minute intervals. The average of the two last readings was used in the analysis. Height and weight were measured with subjects wearing

light clothing and no shoes. BMI was calculated as weight in kilograms, divided by the square of height in meters (kg/m^2). Waist circumference was measured at the umbilical line. Non-fasting blood samples were collected from an 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: Boeringer 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. For measurements of MPV and platelet count, 5 ml blood were drawn into vacutainer tubes, containing EDTA as an anticoagulant (K_3 – EDTA 40 µl, 0.37 mol/L per tube), and analysed within 12 hours in an automated blood cell counter (Coulter Counter®, Coulter Electronics, Luton, UK). Information on self-reported diabetes, current smoking and family history of MI was collected from a self-administered questionnaire. The questionnaire is presented in the appendix.

3.3 Outcome measurements - 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, I81, I82, I67.6, O22.3, O22.5, O87.1, O87.3 for the period 1999-2007. The index of medical diagnoses included diagnoses from outpatient clinic visits and hospitalizations. An additional search through the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE, either as a cause of death (part one of 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 diagnoses. All relevant diagnostic 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. The personnel were blinded to the baseline variables, including family history of MI. 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, 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 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.

4. MAIN RESULTS

4.1 Paper I:

FAMILY HISTORY OF MYOCARDIAL INFARCTION IS AN INDEPENDENT RISK FACTOR FOR VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY.

Familial aggregation of coronary heart disease is a strong and independent risk factor for arterial cardiovascular events. This prospective, population-based study was conducted to determine the impact of cardiovascular risk factors, including family history of MI, on the incidence of VTE. Traditional cardiovascular risk factors and family history of MI were registered in 21 330 subjects, aged 25-96 years, enrolled in the Tromsø Study in 1994-95. First-lifetime VTE-events during follow-up were registered up to September 1st 2007. There were 327 VTE-events of which 138 (42%) occurred unprovoked during a mean of 10.9 years of follow-up. In age- and gender-adjusted analysis, age (HR per decade: 1.97, 95 % CI: 1.82-2.12), gender (men vs. women HR: 1.25, 95 % CI 1.01-1.55), BMI (HR per 3 kg/m^2: 1.21, 95 % CI: 1.13-1.31), and family history of MI (HR: 1.31, 95 % CI: 1.04-1.65) were significantly associated with VTE. Family history of MI remained a significant risk factor for both total and unprovoked VTE in multivariable analysis. Blood pressure, total cholesterol, HDL-cholesterol, triglycerides and smoking were not independently associated with total VTE. HDL-cholesterol was significantly associated with increased risk of unprovoked VTE in multivariable analysis. To the best of our knowledge, this was the first study identifying an association between family history of MI and VTE. In conclusion, family history of MI as an independent risk factor for VTE provides further evidence to the concept of a link between arterial and venous thrombosis. Traditional cardiovascular risk factors did not seem to be underlying determinants for this association, suggesting that family members share yet unknown genetic or environmental risk factors.

4.2 Paper II:

ABDOMINAL OBESITY IS ESSENTIAL FOR THE RISK OF VENOUS THROMBOEMBOLISM IN THE METABOLIC SYNDROME - THE TROMSØ STUDY.

This study was undertaken to investigate whether the metabolic syndrome, and its individual components, was associated with increased risk of venous thromboembolism (VTE). Individual components of the metabolic syndrome were registered in 6170 subjects aged 25 to 84 years who attended the second screening visit of the Tromsø Study in 1994-95, and first lifetime events of VTE were registered until September 1st 2007. The metabolic syndrome was present in 21.9 % (1350 subjects) of the population. There were 194 validated first VTE events (2.92 per 1000 person-years) during a mean of 10.8 years of follow up. Subjects with the metabolic syndrome had increased risk of VTE (HR: 1.65, 95 % CI: 1.22-2.23) in age- and gender-adjusted analysis. Furthermore, the risk of VTE increased with the number of components in the metabolic syndrome ($p<0.001$). Among the individual components of the syndrome, abdominal obesity was the only component significantly associated with VTE in multivariable analysis including age, gender and the other individual components of the syndrome (HR: 2.03, 95% CI: 1.49-2.75). When abdominal obesity was omitted as a diagnostic criterion in a modified definition of the syndrome, none of the other components, alone or in cluster, was associated with increased risk of VTE. In fact, the risk associated with abdominal obesity alone was higher than the risk associated with the metabolic syndrome. In conclusion, this study provided evidence for the metabolic syndrome as a risk factor for VTE. Moreover, abdominal obesity appeared to be the crucial risk factor among the individual components of the syndrome.

4.3 Paper III:

HDL-CHOLESTEROL AND FUTURE RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY.

The purpose of this study was to determine the impact of HDL-cholesterol on VTE risk in a large prospective, population-based study. Risk factors, including HDL-cholesterol, were registered in 26 676 subjects, aged 25-96 years, enrolled in the Tromsø Study in 1994-95, and incident VTE events were registered during follow-up until 1 September 2007. There were 458 VTE events of which 191 (41.7 %) occurred unprovoked. HDL-cholesterol was not associated with risk of total VTE. The multivariable-adjusted HR per 0.5 mmol/L HDL-cholesterol was 1.08 (95 % CI: 0.93-1.26) in women and 1.10 (95 % CI: 0.91-1.32) in men. When analysing unprovoked VTE separately, multivariable-adjusted HR per 0.5 mmol/L HDL-cholesterol was 1.39 (95 % CI: 1.10-1.75) in women and 1.15 (95 % CI: 0.87-1.53) in men. HRs by quartiles of HDL-cholesterol revealed that women in the upper quartile had significantly 1.87-fold (95 % CI: 1.01-3.47) increased risk of unprovoked VTE compared to subjects in the lowest quartile (p for trend across quartiles=0.03). There was no significant trend (p=0.2) across HDL-cholesterol quartiles in men. In conclusion, our findings challenge the concept that high HDL-cholesterol protects against venous thrombosis. Further studies are needed to determine whether the apparent increased risk of unprovoked VTE by HDL-cholesterol in women is a direct effect of HDL or due to unrecognized confounders.

4.4 Paper IV:

MEAN PLATELET VOLUME IS AN INDEPENDENT RISK FACTOR FOR VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

The purpose of the study was to determine the impact of platelet count and platelet size, measured as MPV, on the incidence of VTE in a prospective, population-based study. Platelet count, MPV and baseline characteristics were registered in 25 923 subjects aged 25 to 96 years, who participated in the fourth survey of the Tromsø Study in 1994-95. Incident VTE-events were registered through end of follow-up (September 1, 2007). During the study period there were 445 validated incident VTE events (1.6 per 1000 person-years), of which 186 (42%) were unprovoked. Mean follow-up time was 10.8 years. Increasing levels of MPV was associated with increased risk of total VTE (p for trend=0.09), and unprovoked VTE (p for trend=0.03) in analysis adjusted for age and sex. Subjects with MPV ≥9.5 fL had a 1.3-fold (95% CI: 1.0-1.7) higher risk of total VTE, and a 1.5-fold (95% CI: 1.1-2.3) higher risk of unprovoked VTE compared to subjects with MPV<8.5 fL in analysis adjusted for age, sex, smoking, BMI and platelet count. There was no significant association between increasing platelet count and risk of VTE. In conclusion, increasing levels of MPV was identified as a predictor for VTE, in particular VTE of unprovoked origin. The present findings support the concept that platelet reactivity is important in the pathogenesis of venous thromboembolism.

5. GENERAL DISCUSSION

5.1 Methodological considerations

Study design

The four papers presented in this thesis are all based on a large prospective cohort study. Cohort studies have several advantages. First, there is the clear temporal sequence of exposure and outcome, which is essential to establish some indication of causality. Second, the cohort study is more likely to obtain valid and unbiased information on the subject's exposure compared to a retrospective study. Another advantage of cohort studies is the large number of study subjects, which enhances the generalizability and external validity. Cohort studies are usually ethically safe due to their non-experimental nature. A problem with the cohort method occurs when the incidence of disease is low, and large numbers of people must be followed up for long periods before sufficient cases accrue to give statistically meaningful results.

Cohort studies have major advantages compared to case-control studies in measuring possible associations between exposure and disease. The retrospective nature of case-control studies results in an indecisive sequence of exposure and outcome, and it cannot be definitely established whether the associated variable is a response to rather than a cause of the disease. Validation of information on exposure may be difficult, and there is a risk of recall bias particularly related to self-reported exposure. A case-control study can generate a hypothesis of causality, but can not be used to establish a cause-and-effect relationship.

Cohort studies are similar to randomised controlled trials (RCT) in that they compare outcomes in subjects who have or have not been exposed to a variable of interest. The main difference is that in cohort studies, allocation of individuals is not by chance. Thus, one cannot definitely establish whether the observed difference in outcomes between the two comparison groups is attributed to the exposure rather than other factors (confounders). According to the Bradford-Hill criteria of causality [120], a cause-and-effect relationship

depends on a temporal relationship, the strength of the association, and that there is a dose-response relationship between exposure and risk. All these factors can be assessed by a cohort study. However, the Bradford-Hill criteria also require experimental evidence for assessment of causality, i.e. that the outcome can be altered by an appropriate experimental regimen altering exposure. The cohort is insufficient in this matter. Thus, the cohort study can be used to measure associations, but not establish causality.

The RCT is the gold standard for establishing cause-and-effect relationships. RCTs are experimental comparison studies in which participants are allocated to intervention or control groups using a random mechanism. In our cohort study, we found a strong and independent association between obesity and VTE. Thus, an appropriate way to further examine a cause-and-effect relationship between obesity and VTE would be to conduct a RCT investigating the impact of weight reduction on risk of VTE. The drawbacks of RCTs are that they are expensive and time consuming, and can sometimes be ethically problematic. The generalizability of a RCT can also be limited due to very strict inclusion and exclusion criteria. For some conditions, RCTs are not suitable, and cohort studies remain the best alternative for investigating possible exposure-outcome relations.

Generalizability

The findings of a study are generalizable if the results are applicable to other populations. The Tromsø study is based on a general adult population. All inhabitants in the municipality of Tromsø aged 25 or older were invited to our study, and the attendance rate was high; 77 % of the eligible population participated. The age and sex distribution of the Tromsø population is not substantially different from Western populations regarding the incidence and prevalence of cardiovascular diseases, educational levels, and social and lifestyle factors. The incidence of VTE found in our study is comparable to other Western

populations [44,121]. Even though our study population was recruited from a general population with high attendance rate, selection bias due to lower attendance rate in severely ill and disabled individuals is likely to have occurred. Furthermore, the age-specific attendance rates where somewhat lower in the younger (<40 years) and older (≥80 years) age groups, and this may influence the representativeness of the results for these age groups.

Confounding

In cohort studies, confounding is a potential problem for assessment of causality [122]. Ideally, the comparison groups in a cohort study should be identical apart from the exposure variable of interest. However, in reality this situation does not exist due to the non-randomized nature of cohorts [123]. A confounding factor is a factor that is related to both the exposure and outcome; or more exactly, a factor that differs between the comparison groups and predicts the outcome variable [122,124]. Confounding can cause bias in either directions; both over- and underestimate the actual effect. Bias introduced by confounding can also occasionally be strong enough to reverse the apparent direction of an effect [125].

Stratification and multivariable analysis are strategies to control or minimize confounding [126]. Stratification describes a process where the sample is divided into subgroups on the basis of characteristics thought to confound the analysis. This method was used in paper III. Subjects were stratified by gender as levels of HDL-cholesterol are known to differ in men and women. Multivariable analysis is a statistical tool for determining the independent contribution of each risk factor to a single outcome [124]. In paper I, risk estimates for VTE were presented in age- and gender-adjusted analysis, as well as in a multivariable model including all the potential cardiovascular risk factors examined in the

study. Likewise, in paper IV risk estimates were adjusted for age and gender and in a multivariable model including other potential confounders.

Even if a confounder is known, there may be insufficient data to evaluate it. In our study we did not have baseline information on inherited thrombophilic disorders, which are, of course, potential confounders. However, information on thrombophilic factors measured in the VTE-patients at the time of the event, revealed that one or more thrombophilic factor (APC-resistance, protein C-, protein S- or antithrombin-deficiency or lupus anticoagulant) was present in only 16 % of those with an unprovoked event, suggesting that most of the unprovoked events apparently was caused by other risk factors. We are not aware of any publications that have established an interrelation between inherited thrombophilic disorders and the risk factors investigated in papers I-IV. Thus, we do not believe that inherited thrombophilic disorders represent unrecognized confounders in our study.

Misclassification and information bias

Although cohort studies allow complete and validated baseline data, sometimes exposure information can be sparse because the large number of subjects does not permit long interviews, and questionnaires can be difficult to complete properly. Erroneous information from study subjects can produce systematic error in studies. Misclassification of subjects for either exposure or disease can be differential (related to the occurrence of disease) or nondifferential (not related to occurrence of disease). In a prospective cohort study, exposure is measured before the development of disease, and hence exposure-misclassification is generally nondifferential.

Self-reported data is a possible source to misclassification. In our study, self-reported dichotomous data collected from the questionnaire included diabetes, smoking and family history of disease. Both underreporting and overreporting of these variables are possible.

Current guidelines provide established cut-off values for diabetes mellitus based on fasting blood glucose levels [127]. The prevalence of diabetes type 2 is reported to be approximately 10 %, and is increasing in western countries [128]. Screening for type 2 diabetes is not carried out on a regular basis, and it is likely that a number of subjects are undiagnosed according to the established criteria [129]. The prevalence of self-reported diabetes in our study was lower than 2 %, which is substantially lower than expected. Thus, it is likely that self-reported diabetes in our study provides an underestimate of the true prevalence for diabetes. When completing questionnaires, study subjects may wish to report behaviours consistent with a healthy lifestyle. Self-report of smoking has been shown to underestimate the true prevalence in some studies [130,131], whereas others have found self-reported smoking status to be reasonably valid [132]. In a validation study on the reliability of reported family history of MI, Kee at al. demonstrated a high specificity (97 %) and a somewhat lower sensitivity (68 %) of reporting a positive family history of MI [133]. Thus, underestimation of the risk associated with family history of MI is more likely.

In our study, blood samples for measurement of serum lipid levels were drawn in a non-fasting state between 08.00 hours and 20.00 hours. The use of non-fasting blood samples may represent another possible source of misclassification, as current guidelines recommend measurement of a fasting lipid profile for assessment of cardiovascular risk [59]. However, total cholesterol and HDL-cholesterol does not exhibit any substantial diurnal variation [134] or postprandial changes [135-137], and thus we believe that the use on non-fasting samples had negligible impact on our results regarding cholesterol. In contrast, triglyceride levels vary substantially during the day [134] and increases significantly following a high-fat meal [137], suggesting that fasting levels are recommended. On the other hand, the fasted state is a relatively artificial metabolic condition as our body spends most of the day in a postprandial environment. Thus, one might argue that non-fasting lipid levels possibly represent a more

accurate assessment of lipid status. Recently, a study by Mora et al. [138] reported that associations with CVD was similar for fasting and non-fasting total cholesterol and HDL-cholesterol, and stronger for non-fasting triglycerides compared to fasting values, suggesting that non-fasting lipid samples are preferable for assessment of CVD-risk.

Modifiable risk factors

The optimal follow-up time for detection of outcome after exposure may vary due to the causal mechanism and biology of the disease. Modifiable risk factors are a potential limitation of cohort-studies, especially when the time between exposure and disease manifestation is very long. In our study, subjects were followed for a mean of 10.8 years (median 12.5), and the individual risk profile may have changed during this period in some subjects, as most of the cardiovascular risk factors are modifiable. This kind of misclassification generally leads to underestimation of the associated risk, due to regression dilution bias [139].

Missing values

Missing observations are quite common in large cohorts. Missing may be due to various reasons, e.g. subjects do not respond adequately to questionnaires, subjects are lost to follow-up, occasional missing values because some equipment failed during measurements, or laboratory samples are lost in transition or technically unsatisfactory [140]. The question of how to handle missing data is controversial, and there are various approaches on how to handle missing data in analysis. One alternative is to omit variables with many missing data. Another approach is to omit individuals who do not have complete data, which is probably the most common method [140]. The third alternative is to use imputation techniques to replace

missing values. In general, imputation techniques are based on replacement of missing values by a plausible value predicted from an individual's available dataset.

The main concern is whether the presence of missing has introduced bias. In paper I presented in this thesis, about 20 % of the participants did not complete the questions on family history of MI. We chose to do available-case analysis, and subjects with missing values were excluded from the study population. An important question to investigate was whether the study population (available-case population) differed from the source population. In order to assess the representativeness of the study population, we compared the risk estimates (HRs) for all traditional cardiovascular risk factors other than family history of MI in the study population and the source population. The HRs for each of the other traditional cardiovascular risk factors were essentially identical in the two populations, implying that the study population presumably was representative for the source population. We also explored the extremes of our missing data on family history of MI, by performing analysis where we assumed that the answer of all non-responders was negative. In these analyses the risk estimate for family history of MI was slightly attenuated, as expected, but it was still increased, and considered strong enough to support our assumptions of a robust association.

Detection and validation of outcome

In our study, VTE-events among the study participants during follow-up were registered retrospectively by using the medical diagnostic index, the radiology procedure register, and the autopsy register at the University Hospital of North-Norway. This hospital exclusively provides health care services to the inhabitants in the Tromsø municipality, which enhances the probability of a complete VTE-register. However, some cases of VTE can possibly have been missed if they were diagnosed and treated elsewhere. In order to make the manifestation of disease as certain as possible, our validation of outcome was dependent on four solid

criteria. The VTE-event should be (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral-CT, perfusion-ventilation scan, pulmonary angiography or autopsy) and (ii) the medical record should indicate that a physician had made a diagnosis of DVT or PE. Furthermore, (iii) signs and symptoms consistent with DVT or PE should be present, and (iv) the patient should receive therapy with anticoagulants (heparin, warfarin, or a similar agent) thrombolytics or vascular surgery, unless a specific reason for not providing treatment were specified in the medical record. We wanted to ensure that all cases were significant and incident clinical events and the four criteria were combined in order to avoid false positive VTE-cases. For instance, by using these criteria, an asymptomatic venous thrombi of undefined age accidentally discovered by computed tomography and not treated with anticoagulants (or similar agent) would not be considered a clinical event.

Despite the use of firm criteria for outcome validation, misclassification of VTE-cases cannot be completely ruled out. Retrospective registration is dependent on valid and complete information, and thus insufficient information from patient records could lead to inaccuracy. Furthermore, there were no standard instructions for reporting presence of clinical risk factors and provoking factors for VTE in the medical record, and classification of events as unprovoked or provoked relied on information provided by the individual physician who examined the VTE-patient. Since the personnel who registered the VTE-events were blinded to the baseline information, any misclassification of VTE was most likely nondifferential. Nondifferential outcome misclassification generally leads to underestimation of the true outcome-exposure association [125]. This is in contrast to differential outcome misclassification which could introduce a false positive/negative outcome-exposure association.

Unfortunately, we did not have verified baseline information on previous history of VTE among the study-subjects. Hence, some of the subjects who were treated as healthy

participants during follow-up could be prevalent VTE-cases who should have been excluded from the study population. However, this would lead to only a small change in the overall number of person-years at risk, and thus would presumably have a negligible influence on the risk estimates.

5.2 Discussion of main results

Serum lipid levels and VTE

Dyslipidemia is associated with hypercoagulability, endothelial dysfunction and increased platelet aggregation [57,141,142]. An unfavourable lipid profile, including high levels of triglycerides, high LDL-cholesterol and low HDL-cholesterol, is a well established risk factor for development of atherosclerosis and arterial cardiovascular disease.

In the recent years, there has been increasing interest in investigating the possible relationship between serum lipid levels and risk of venous thrombosis. High levels of triglycerides [57,98,143] and lipoprotein A [144,145] have been associated with increased risk of VTE in case-control studies. A retrospective cohort study of 125 862 men and women aged ≥ 65 years reported a 22% relative risk reduction in the risk of DVT among statin users [146]. Recently, a RCT showed that 20 mg rosuvastatin daily significantly reduced the occurrence of symptomatic VTE [147]. However, the risk-reduction appeared to be independent of lipid status [147], suggesting that the effect was caused by other antithrombotic properties of statins [148]. In our study, elevated triglyceride levels (paper I and II) and total cholesterol (paper I) showed no association with VTE. These findings are in agreement with both the LITE-cohort [11] and the cohort of Swedish men [15].

Whether isolated hypertriglyceridemia is atherogenic in the absence of either increased LDL-cholesterol or decreased HDL-cholesterol has been a matter of dispute [149]. There is evidence for triglycerides as an independent risk factor for CAD in certain subgroups, but the

evidence for triglycerides as a synergistic CAD risk factor is stronger [149]. In our study, we investigated whether triglycerides were independently associated with VTE. For further research, a comparison study on risk factors for VTE and CAD within the same population is probably useful to determine and compare the impact of triglycerides and cholesterol on the individual prediction of these conditions. Another interesting approach is to investigate the relationship between postprandial hyperlipidemia and VTE, as postprandial hyperlipidemia may prove a better indicator of atherogenicity [150].

Low HDL-cholesterol is an established risk factor for CAD [76], a concept supported by the antiatherogenic and antithrombotic properties of HDL [78,88]. Several case-control studies [56,57,97] and a prospective cohort study [55] have suggested that high levels of HDL-cholesterol are protective against VTE. However, other prospective studies have failed to show this relationship [11]. Low HDL-cholesterol was not associated with risk of VTE in our population (paper II and III). In fact, high levels of HDL-cholesterol were apparently associated with increased risk of unprovoked VTE in women, a finding supported by data from the LITE cohort study [101] and the Women's Health Study [151]. The apparent inconsistency between the abovementioned studies may rely on several methodological factors. The nature of case-control studies does not allow determining whether the observed HDL-cholesterol level is a response to rather than a cause of VTE. Inflammatory markers, such as fibrinogen, C-reactive protein (CRP) and white blood cell count, has not been associated with future risk of VTE [152], but VTE is associated with elevated serum levels of high sensitivity-CRP (hs-CRP) after the acute event [153], and hs-CRP is known to be an inverse predictor of HDL-cholesterol [154]. Similarly to acute CAD [155,156], it is likely to assume that HDL-cholesterol would decline following an acute VTE-event. In the largest case-control study among postmenopausal women, HDL-cholesterol was measured prior to the VTE event and showed no significant association between HDL-cholesterol and risk of

VTE in quartile-based analysis and adjusted odds ratios [57]. Similarly, low HDL-cholesterol was not associated with increased risk of VTE in young women after adjustment for BMI [99]. A third case-control study reported only an inverse association between HDL-cholesterol and VTE risk in the lowest tentile of HDL-cholesterol in men, but not in women [98]. The strongest association between HDL-cholesterol and risk of VTE appeared in a 1:1 matched case-control study among 49 male VTE patients less than 55 years of age in which controls were recruited among healthy blood donators and not from the general population [56]. The prospective cohort study [55] reported significantly lower crude HDL-cholesterol at baseline among subjects who developed VTE during 23 years of follow-up. However, no risk estimates for VTE was presented, neither in crude nor adjusted analysis, and thus potential confounders for this observed relationship could not be assessed [55]. In summary, the methodological considerations of the studies reporting an inverse relation between HDL-cholesterol and risk of VTE weaken the evidence in favour of HDL-cholesterol as a protective factor for venous thrombosis.

In our study, HDL-cholesterol was apparently positively associated with increased risk of unprovoked VTE in women, and a similar tendency was found in the LITE-study [101]. Estrogen supplementation is known to increase HDL-cholesterol [157] and the risk of VTE [158,159]. However, the increased risk of VTE by HDL-cholesterol in women was probably not explained by estrogen supplementation or menopausal status as adjustment for these variables did not attenuate the HR. The antithrombotic properties of HDL particles may imply that HDL-cholesterol is a marker rather than a mediator of increased risk of unprovoked VTE, particularly among women. Further studies are warranted to determine whether the apparent increased risk of unprovoked VTE by HDL-cholesterol in women is a direct effect of HDL or due to unrecognized confounders.

Serum lipid levels including total cholesterol, triglycerides and HDL-cholesterol (inverse) are related to risk of atherosclerosis and development of arterial cardiovascular disease. In the recent years, increasing evidence suggest a link between arterial and venous thrombosis, possibly through the pathophysiological process of atherosclerosis, or the sharing of common risk factors [45,52,54]. Based on the existing literature and the present findings of our study, we conclude that serum lipid levels, including total cholesterol, HDL-cholesterol and triglycerides, are not independently associated with risk of VTE, and that the apparent relationship between arterial and venous thrombosis probably is due to other risk factors or mechanisms. On the other hand, postprandial lipemia as a risk factor for VTE cannot be ruled out. Experimental studies have shown that very low density lipoprotein (VLDL) enhances prothrombin activation by factor Xa in the presence of factor Va [160,161]. Studies in healthy individuals and patients with combined hyperlipidemia have reported increased coagulation activation, assessed by plasma levels of activated factor VII [162-165] and endogenous thrombin generation [164], during the postprandial state. Moreover, dietary low fat intake [166], intervention with polyunsaturated n-3 fatty acids supplementation [163,164] and cholesterol-lowering treatment [163,164] is reported to decrease coagulation activation during the postprandial phase. So far, no study has investigated the impact of postprandial hyperlipidemia on VTE. Attention should be drawn to investigate this relationship in the future.

Other cardiovascular risk factors and VTE

Age, BMI, family history of MI and MPV were recognized as risk factors for VTE in the papers (I-IV) presented in this thesis, whereas serum lipid levels, smoking, hypertension and diabetes showed no association with VTE. The metabolic syndrome was significantly

associated with VTE, but this association was fundamentally dependent on the presence of obesity.

Smoking is a well known risk factor for MI and stroke [167]. In agreement with other prospective studies [5,11], there were no association between smoking, expressed as a dichotomous variable (current smoking yes/no), and VTE in our study (paper I). Heavy smoking has been associated with increased risk of PE in women [14] and VTE in men [15]. Investigating various degrees of smoking may be a better approach to assess the possible relationship between smoking and risk of VTE in the future.

Hypertension defined by the NCEP-ATPIII criteria was not associated with VTE in our study (paper II). Likewise, neither systolic nor diastolic blood pressure showed any relation with increased risk of VTE (paper I). The Nurses' Health Study found that self-reported hypertension was related to increased risk of PE [14], and the Copenhagen City Heart Study reported a higher crude proportion of baseline hypertension in subjects with VTE [55]. However, in agreement with our results, most prospective studies including the LITE-study [11], the Physicians' Health Study [5] and the cohort of Swedish men [15] found no relationship between blood pressure and VTE, suggesting that hypertension is not an independent risk factor for venous thrombosis.

Previous reports from prospective studies are conflicting with regard to the impact of diabetes on risk of VTE. The LITE-study [11] reported that diabetes was associated with increased risk of VTE, whereas the Physicians' Health Study [5] and the Nurses Health Study [14] found no association. In our study (paper I), subjects with self-reported diabetes had a 2.5-fold higher incidence rate of VTE, and a non-significantly 1.4-fold increased risk of VTE. In multivariable analysis including BMI, the association disappeared. Furthermore, impaired glucose tolerance defined as HbA1c $\geq$ 5.6 mmol/L showed no independent association with VTE (paper II). As previously described in this thesis, self-reporting of data enhances the risk

of misclassification, and thus may conceal the magnitude of the true association. Blood glucose levels were not measured in the entire cohort and self-reported diabetes was the only available variable for this condition. In the LITE-cohort, diabetes was defined as fasting glucose levels of ≥7mmol/L, non-fasting glucose levels of ≥11.1 or a history of treatment for diabetes, and the prevalence of diabetes was substantially higher than in our study (11.8 % vs 1.4 %). Regarding diabetes and risk of VTE, the apparent inconsistency between studies may to some extent rely on different diagnostic criteria for diabetes.

Obesity could be a key factor in the observed association between arterial and venous thrombosis. Obesity is clearly related to increased risk of both conditions, however, it is apparently a more important risk factor for VTE compared to arterial events like MI and stroke [5]. In paper II, we demonstrated that obesity was clearly essential for the observed increased risk of VTE associated with the metabolic syndrome. Obesity is associated with raised intra-abdominal pressure and reduced venous blood flow velocity which may render blood more susceptible to thrombosis in the deep veins [168,169]. Furthermore, visceral adipose tissue is highly metabolic active, releasing increased amounts of proinflammatory-, proatherogenic- and prothrombotic substances [170], which may be a common pathophysiological explanation for the observed risk of thrombosis in both the arterial and venous systems.

Familial aggregation of coronary heart disease is a strong and independent risk factor for arterial cardiovascular events [171,172]. We have for the first time identified an association between family history of MI and VTE (paper I). Traditional cardiovascular risk factors, including age, hypertension, serum lipid levels, obesity, smoking and diabetes did not seem to be underlying confounders for this association (paper I).

Atherosclerosis is associated with endothelial dysfunction, coagulation activation and platelet activation [173], with a subsequent increase in risk of arterial thrombosis [174,175]. Family history of cardiovascular disease has previously been identified as a predictor for

subclinical carotid atherosclerosis [176], and to be an independent predictor for coronary calcification in young subjects [177]. Moreover, a higher frequency of carotid plaques [45] and coronary calcification [178,179] has been reported in patients with VTE, and it has also been shown that a first arterial cardiovascular event is associated with subsequent development of VTE [46]. Thus, it is not unreasonable to suggest that a plausible pathophysiological link exist between atherosclerosis and VTE. However, as described in the introduction of this thesis, the impact of subclinical atherosclerosis as a risk factor for VTE is controversial [45-47]. In summary, subclinical atherosclerosis cannot be ruled out as a plausible link between arterial and venous thrombosis, but further research, preferably prospective cohorts of general populations with a wide age range, is essential to establish the true nature of this relationship.

Although atherosclerosis may represent a possible link, the apparent lack of association with traditional cardiovascular risk factors, presented in our work, indicate that also other factors than the atherosclerotic process itself may contribute to the link between arterial and venous thrombosis. Moreover, the sequence of thrombotic events is not predetermined, as patients who have suffered a VTE event, also are reported to have increased risk of an arterial thromboembolic event during long-term follow up [52]. Altogether, these findings suggest that family members share yet unknown genetic or environmental risk factors for VTE.

Platelets are known to play an important role in the formation of thrombi. Platelet size, measured as MPV, is associated with increased platelet reactivity. Increased levels of MPV are found in patients with coronary artery disease [115,116], and MPV has been identified as an independent risk factor for myocardial infarction and stroke [117-119]. In the search for other potentially shared risk factors for arterial and venous thrombosis, we identified MPV as a possible common risk factor (paper IV). To our knowledge, this is the first study showing a

relationship between MPV and VTE. However, several factors support the concept of platelet reactivity as a risk factor for venous thrombosis. Increased levels of platelet activation markers have been reported in patients with PE compared to controls [180]. Furthermore, increased levels of P-selectin have been shown in VTE patients [109,181], and higher circulating P-selectin was associated with increased risk of recurrent VTE in patients with first unprovoked VTE [110]. The identification of MPV as a risk factor for VTE implies that platelets might have a more important role in the pathogenesis of venous thrombosis than previously assumed.

Twin studies have shown high heritability estimates for blood cell size and count [182,183], and results from the Framingham study suggested that heritable factors play a major role in determining platelet aggregation [184]. Moreover, heritability of platelet function in families with premature CAD has been reported [185]. Thus, it might be speculated that platelet reactivity is a possible common risk factor for both arterial and venous thrombosis shared by family members.

A wide range of other blood constituents such as platelets, erythrocytes, leukocytes and inflammatory cytokines, as well as coagulation and fibrinolytic factors are all likely to contribute to, or promote, both arterial and venous thrombogenesis [186]. Cellular microparticles are small membrane vesicles that are released from cells upon activation or apoptosis. Microparticles are considered to constitute the main reservoir of blood-borne tissue factor [187], and circulating microparticles provide an additional procoagulant phospholipid surface enabling the assembly of the clotting enzyme complexes and thrombin generation [188]. Increased levels of circulating microparticles have been reported in cardiovascular diseases such as acute coronary syndrome and stroke [189], and in young survivors of MI [190]. Moreover, elevated levels of endothelial microparticles and platelet-leukocyte conjugates have been reported in VTE patients during the acute phase compared to healthy

controls [109], and platelet derived microparticles were increased in subjects with PE [180]. However, in a case-control study of 116 cases with recurrent VTE, there were no association between circulating microparticles and VTE [191]. Limited data exist on the possible relation between endothelial dysfunction and venous thrombosis. A 1:1 case-control study in 28 cases and controls reported higher levels of plasma von Willebrand factor and impaired endothelial dysfunction, assessed by flow mediated dilation, in subjects with unprovoked VTE [181].

Factors that influence blood viscosity and blood flow, such as hematocrit, may also contribute to risk of thrombosis. Hematocrit levels above the normal population range, such as in primary or secondary polycythemia, are associated with increased risk of both arterial and venous thrombosis [192,193]. High hematocrit has shown significant association with coronary heart disease in some studies of general populations [194], whereas the potential relation to risk of VTE has not been extensively examined in general populations.

In the past few years, results of structural and functional studies have supported a role of inflammation in both arterial and venous thrombosis [195]. However, in the LITE-study there were no association between VTE and inflammation markers such as CRP and leukocytes [152], and mean CRP levels were not related to VTE in the Physicians' Health Study [196]. On the other hand, a few studies suggest that cytokines and chemokines are involved in the pathogenesis of VTE. In a population based case-control study with 474 VTE-patients and 474 healthy controls, elevated levels of interleukin-8 (IL-8) was associated with increased risk of VTE [197], and TNF-alpha, IL-6 and IL-8 levels was found to be determinants of the risk of VTE [198]. Further prospective studies are required to elucidate the role of cellular components and various inflammation markers as common risk factors for arterial and venous thrombosis.

6. CONCLUSIONS

In our prospective population-based study we found that increasing age, BMI and family history of MI were associated with increased risk of VTE. Other traditional cardiovascular risk factors such as blood pressure, serum lipid levels including total cholesterol, HDL-cholesterol and triglycerides, self-reported diabetes and smoking showed no association with VTE. The identification of family history of MI as an independent risk factor for VTE provides further evidence to the concept of a link between arterial and venous thrombosis. Traditional cardiovascular risk factors did not seem to be underlying determinants for this association, suggesting that family members share yet unknown genetic or environmental risk factors.

The metabolic syndrome was associated with increased risk of VTE in our study. When analysing the individual components of the syndrome, abdominal obesity was the only risk factor independently associated with VTE. Impaired glucose tolerance, hypertension, high levels of triglycerides and low HDL-cholesterol showed no association with VTE. Furthermore, our results revealed that abdominal obesity was essential for the observed association between the metabolic syndrome and VTE.

Low HDL-cholesterol was not associated with VTE in our study. In contrast, high levels of HDL-cholesterol were apparently associated with increased risk of unprovoked VTE in women. Our findings challenge the suggested concept that high HDL-cholesterol protects against venous thrombosis. Further studies are needed to determine whether the apparent increased risk of unprovoked VTE by HDL-cholesterol in women is a direct effect of HDL or due to unrecognized confounders.

Increasing levels of MPV was associated with risk of VTE, especially those of unprovoked origin. Platelet count showed no association with neither total nor unprovoked

VTE. The findings of this study support the concept that platelet reactivity is important in the pathogenesis of venous thrombosis.

7. REFERENCES

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Paper I

Paper II

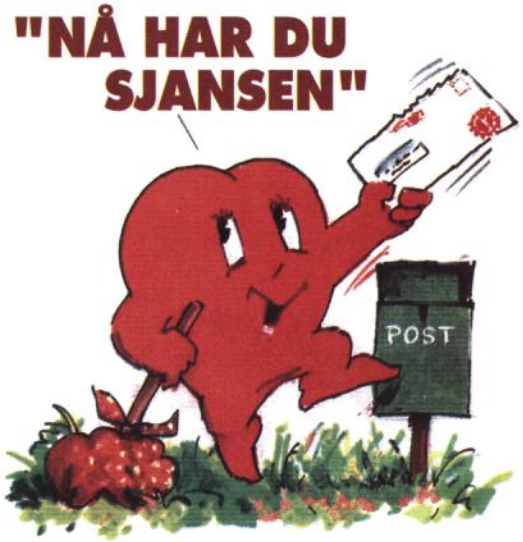
Paper III

Paper IV

Appendix

Innbydelse til

HELSEUNDERSØKELSEN



Fødselsdato	Personnr.	Kommune	Kretsnr.

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.

Undersøkelsen blir mest verdifull om frammøtet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Møt selv om du kjenner deg frisk, om du er under legebehandling, eller om du har fått målt kolesterol og blodtrykk i den senere tid.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

EGEN HELSE

Hvordan er helsen din nå? *Sett bare ett kryss.*

Dårlig	12	1
Ikke helt god		2
God		3
Svært god		4

Har du, eller har du hatt:

	JA	NEI	Alder første gang
Hjerteinfarkt 13			år
Angina pectoris (hjertekrampe) 16			år
Hjerneslag/hjerneblødning 19			år
Astma 22			år
Diabetes (sukkersyke) 25			år

Bruker du medisin mot høyt blodtrykk?

Nå	28	1
Før, men ikke nå		2
Aldri brukt		3

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 29 — JA / NEI

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig? 30				
Plaget av angst? 31				
Trygg og rolig? 32				
Irritabel? 33				
Glad og optimistisk? 34				
Nedfor/deprimert? 35				
Ensom? 36				
	1	2	3	4

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 37 — JA / NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 38 — JA / NEI

Hvis "JA", hvor mange år tilsammen? 39 — Antall år

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? 41 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig? 43		
Sigarer/sigarillos daglig? 44		
Pipe daglig? 45		

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 46 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 48 — Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 52 — Alder år

Hvor mange år tilsammen har du røykt daglig? 54 — Antall år

MOSJON

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

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* 56				
Hard fysisk aktivitet *(svett/andpusten)* 57				
	1	2	3	4

KAFFE

Hvor mange kopper kaffe drikker du daglig?
Sett 0 hvis du ikke drikker kaffe daglig.

Kokekaffe	58	Antall kopper
Annen kaffe	60	Antall kopper

ALKOHOL

Er du total avholdsmann/-kvinne? 62 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. 63 — Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65
Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

Øl	Vin	Brennevin
glass	glass	glass

FETT

Hva slags margarin eller smør bruker du vanligvis på brødet? *Sett ett kryss.*

Bruker ikke smør/margarin	71	1
Meierismør		2
Hard margarin		3
Bløt (soft) margarin		4
Smør/margarin blanding		5
Lettmargarin		6

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole	72	1
Realskole, middelskole, yrkesskole, 1-2-årig videregående skole		2
Artium, øk.gymnas, allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

Hva slags arbeidssituasjon har du nå?

Lønnet arbeid	73	
Heltids husarbeid	74	
Utdanning, militærtjeneste	75	
Arbeidsledig, permittert	76	

Hvor mange timer lønnet arbeid har du i uka? 77 — Antall timer

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	79	
Attføring	80	
Uførepensjon	81	
Alderspensjon	82	
Sosialstøtte	83	
Arbeidsløshetstrygd	84	

SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 85 — JA / NEI / VET IKKE

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 kreftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. 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 komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite 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 purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dag Mnd År

Dato for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 - 28

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

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑
- Gode ..... ❑
- Vanskelige ..... ❑
- Meget vanskelige ..... ❑

Hvor mange av de første 3 årene av ditt liv
- bodde du i by? ..... 30 _____ år
- hadde dere katt eller hund i hjemmet? ..... 31 _____ år

Hvor mange av de første 15 årene av ditt liv
- bodde du i by? ..... 32 _____ år
- hadde dere katt eller hund i hjemmet? ..... 34 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.		Ja	Nei	Antall
Ektefelle/samboer	36	❑	❑	
Andre personer over 18 år	37	❑	❑	_____
Personer under 18 år	40	❑	❑	_____

Hvor mange av barna har plass i barnehage? ..... 43 _____

Hvilken type bolig bor du i?
- Enebolig/villa ..... 45 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor stor er din boenhet? ..... 46 _____ m^2

I omtrent hvilket år ble boligen bygget? ..... 49 _____

		Ja	Nei
Er boligen isolert etter 1970?	53	❑	❑
Bor du i underetasje/kjeller?	54	❑	❑
Hvis "Ja", er gulvbelegget lagt på betong?	55	❑	❑

Hvordan er boligen hovedsakelig oppvarmet?
- Elektrisk oppvarming ..... 56 ❑
- Vedfyring ..... ❑
- Sentralvarmeanlegg oppvarmet med:
  - Parafin ..... ❑
  - Elektrisitet ..... ❑

		Ja	Nei
Er det heldekkende tepper i stua?	60	❑	❑
Er det katt i boligen?	61	❑	❑
Er det hund i boligen?	62	❑	❑

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?
- For det meste stillesittende arbeid? ..... 63 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?
- Nei, ikke i det hele tatt ..... 64 ❑ 1
- I liten grad ..... ❑ 2
- Ja, i stor grad ..... ❑ 3
- Ja, det bestemmer jeg selv ..... ❑ 4

		Ja	Nei
Har du skiftarbeid, nattarbeid eller går vakter?	65	❑	❑

Har du noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.		Ja	Nei
Sjåfør	66	❑	❑
Bonde/gårdbruker		❑	❑
Fisker		❑	❑

EGNE SYKDOMMER

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

	Ja	Nei	Alder
Lårhalsbrudd 69	❑	❑	_____
Brudd ved håndledd/underarm 72	❑	❑	_____
Nakkesleng (whiplash) 75	❑	❑	_____
Skade som førte til sykehusinnleggelse 78	❑	❑	_____
Sår på magesekken 81	❑	❑	_____
Sår på tolvfingertarmen 84	❑	❑	_____
Magesår-operasjon 87	❑	❑	_____
Operasjon på halsen 90	❑	❑	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 93	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis	❑	❑
Benskjørhet (osteoporose) 98	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren	❑	❑
Nyrestein 103	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue	❑	❑
Matvareallergi 108	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? ..110 ____ ganger

	Ja	Nei
Har du hatt dette siste 14 dager? 112	❑	❑

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.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 113	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 119	❑	❑	❑	❑	❑	❑
Kreftsykdom 125	❑	❑	❑	❑	❑	❑
Astma 131	❑	❑	❑	❑	❑	❑
Mage/tolvfingertarm-sår 137	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 143	❑	❑	❑	❑	❑	❑
Psykiske plager 149	❑	❑	❑	❑	❑	❑
Allergi 155	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 161	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 167	____	____	____	____	____	____

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 177	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 178	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 179	❑	❑
Har du hatt episoder med piping i brystet? 180	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 181	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 185	❑	❑

Hvor ofte er du plaget av søvnløshet?

Aldri, eller noen få ganger i året 186	❑ 1
1-2 ganger i måneden	❑ 2
Omtrent en gang i uken	❑ 3
Mer enn en gang i uken	❑ 4

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

Ingen spesiell tid 187	❑ 1
Særlig i mørketiden	❑ 2
Særlig i midnattsoltiden	❑ 3
Særlig vår og høst	❑ 4

	Ja	Nei
Har du det siste året vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 188	❑	❑

Hvor ofte er du plaget av hodepine?

Sjelden eller aldri 189	❑ 1
En eller flere ganger i måneden	❑ 2
En eller flere ganger i uken	❑ 3
Daglig	❑ 4

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

Ikke i det hele tatt 190	❑ 1
Bare i liten grad	❑ 2
En del	❑ 3
Ganske mye	❑ 4

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
*Sett **0** hvis du **ikke** har hatt slik kontakt.*

	Antall ganger siste år
Hos vanlig lege/legevakt 191	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 197	_____
Innlagt i sykehus	_____
Hos bedriftslege	_____
Hos fysioterapeut 203	_____
Hos kiropraktor	_____
Hos akupunktør	_____
Hos tannlege 209	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
*Sett **0** hvis du **ikke** har brukt midlene.*

Legemidler
- Smertestillende ....215 _____ mnd.
- Sovemedisin .... _____ mnd.
- Beroligende midler .... _____ mnd.
- Medisin mot depresjon ....221 _____ mnd.
- Allergimedisin .... _____ mnd.
- Astmamedisin .... _____ mnd.

Kosttilskudd
- Jerntabletter ....227 _____ mnd.
- Kalktabletter eller benmel .... _____ mnd.
- Vitamin D-tilskudd .... _____ mnd.
- Andre vitamintilskudd ....233 _____ mnd.
- Tran eller fiskeoljekapsler .... _____ mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?
*Sett **ett** kryss for **hvert** spørsmål.*

	Ja	Nei
Legemidler		
Smertestillende medisin 237	❑	❑
Febersenkende medisin	❑	❑
Migrenemedisin	❑	❑
Eksemsalve	❑	❑
Hjertemedisin (ikke blodtrykksmedisin)	❑	❑
Kolesterolsenkende medisin 242	❑	❑
Sovemedisin	❑	❑
Beroligende medisin	❑	❑
Medisin mot depresjon	❑	❑
Annen nervemedisin	❑	❑
Syrenøytraliserende midler 247	❑	❑
Magesårsmedisin	❑	❑
Insulin	❑	❑
Tabletter mot diabetes (sukkersyke)	❑	❑
Tabletter mot lavt stoffskifte (thyroxin)	❑	❑
Kortisontabletter 252	❑	❑
Annen medisin	❑	❑
Kosttilskudd		
Jerntabletter	❑	❑
Kalktabletter eller benmel	❑	❑
Vitamin D-tilskudd	❑	❑
Andre vitamintilskudd 257	❑	❑
Tran eller fiskeoljekapsler	❑	❑

VENNER

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ....259 ____ gode venner
Tell ikke med de du bor sammen med, men ta med andre slektninger!

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

	Ja	Nei
Føler du at du har nok gode venner? 263	❑	❑

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ....264 ❑ 1
- 1-2 ganger i måneden .... ❑ 2
- Omtrent en gang i uken .... ❑ 3
- Mer enn en gang i uken .... ❑ 4

KOSTVANER

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

Den rekker til omtrent ....265 _____ skiver

Hva slags fett blir vanligvis brukt til **matlaging** (ikke på brødet) i din husholdning?
- Meierismør ....266 ❑
- Hard margarin .... ❑
- Bløt (Soft) margarin .... ❑
- Smør/margarin blanding .... ❑
- Oljer ....270 ❑

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss!

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 271	❑	❑	❑	❑ 275

Hvor mye (i **antall** glass, kopper, poteter eller brødskiver) spiser eller drikker du vanligvis **daglig** av følgende matvarer?
*Kryss av for **alle** matvarene.*

	0	Færre enn 1	1-2	3-4	5-6	Mer enn 6
Helmelk (søt eller sur) (glass) 276	❑	❑	❑	❑	❑	❑
Lettmelk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Skummet melk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Te (kopper)	❑	❑	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑	❑	❑
Poteter 281	❑	❑	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød)	❑	❑	❑	❑	❑	❑
Brødskiver med						
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑	❑	❑
– magert kjøttpålegg (f.eks. skinke)	❑	❑	❑	❑	❑	❑
– fetere kjøttpålegg (f.eks. salami)	❑	❑	❑	❑	❑	❑
– gulost 286	❑	❑	❑	❑	❑	❑
– brunost	❑	❑	❑	❑	❑	❑
– kaviar	❑	❑	❑	❑	❑	❑
– syltetøy og annet søtt pålegg	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Hvor mange **ganger i uka** spiser du vanligvis følgende matvarer?
*Kryss av for **alle** matvarene.*

	Aldri	Færre enn 1	1	2-3	4-5	Omtrent daglig
Yoghurt 290	❑	❑	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑	❑	❑
Middag med						
– rent kjøtt	❑	❑	❑	❑	❑	❑
– pølser/kjøttpudding/-kaker	❑	❑	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer) 295	❑	❑	❑	❑	❑	❑
– mager fisk (f.eks. torsk)	❑	❑	❑	❑	❑	❑
– fiskeboller/-pudding/-kaker	❑	❑	❑	❑	❑	❑
– grønnsaker	❑	❑	❑	❑	❑	❑
Majones, remulade o.l.	❑	❑	❑	❑	❑	❑
Gulrøtter 300	❑	❑	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑	❑	❑
Appelsiner, mandariner o.l.	❑	❑	❑	❑	❑	❑
Sukkerholdige leskedrikker	❑	❑	❑	❑	❑	❑
Sukkerfrie («Light») leskedrikker	❑	❑	❑	❑	❑	❑
Sjokolade	❑	❑	❑	❑	❑	❑
Vafler, kaker o.l. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	❑ 308	❑	❑ 1
1-2 ganger i måneden	❑	❑	❑ 2
Omtrent 1 gang i uken	❑	❑	❑ 3
2-3 ganger i uken	❑	❑	❑ 4
Omtrent hver dag	❑	❑	❑ 5 310

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?

- Ikke siste år ..... 311 ❑ 1
- Noen få ganger ..... ❑ 2
- 1 - 2 ganger per måned ..... ❑ 3
- 1 - 2 ganger i uken ..... ❑ 4
- 3 eller flere ganger i uken ..... ❑ 5

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? Sett **0** hvis ingen forsøk.

- – før 20 år ..... 314 _____ ganger
- – senere ..... 316 _____ ganger

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

- – før 20 år ..... 318 _____ kg
- – senere ..... 320 _____ kg

Hvilken vekt ville du være tilfreds med (din "trivselsvekt")? ..... 322 _____ kg

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

- Aldri ..... 325 ❑ 1
- Ikke mer enn en gang i måneden ..... ❑ 2
- To eller flere ganger i måneden ..... ❑ 3
- Ukentlig eller oftere ..... ❑ 4

Dine kommentarer:

BESVARES BARE AV KVINNER

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 blødningsfri i minst 6 måneder? 330	Ja ❑	Nei ❑

Hvis "Ja", hvor mange ganger? ..... 331 _____ ganger

Hvis du fremdeles har menstruasjon eller er gravid:

Hvilken dato startet din siste menstruasjon? ..... 333 dag/ mnd/ år ___/___/___

Bruker du vanligvis smertestillende legemidler for å dempe menstruasjonsplager? 339	Ja ❑	Nei ❑

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Er du gravid nå? 342	Ja ❑	Nei ❑	Usikker ❑

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? 343	Ja ❑	Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 344	❑	❑
Eggehvite i urinen 346	❑	❑

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

Barn:	Fødselsår:	Antall måneder med amming:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

PREVENSJON OG ØSTROGEN

Bruker du, eller har du brukt:	Nå	Før	Aldri
P-pille (også minipille) 372	❑	❑	❑
Hormonspiral	❑	❑	❑
Østrogen (tabletter eller plaster) 374	❑	❑	❑
Østrogen (krem eller stikkpiller)	❑ 1	❑ 2	❑ 3

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå?

376 .....

Hvis du bruker eller har brukt p-pille:

Alder da du begynte med P-piller? ..... 380 _____ år

Hvor mange år har du tilsammen brukt P-piller? ..... 382 _____ år

Dersom du har født, hvor mange år brukte du P-piller før første fødsel? ..... 384 _____ år

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? ..... 386 _____ år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. De skal også øke kunnskapen om kreftsykdommer og alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Endelig skal de gi kunnskap om hvorledes den eldste delen av befolkningen har det. Vi ber deg derfor svare på spørsmålene nedenfor.

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

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dato for utfylling av skjema: ..... 18 Dag ...../ Mnd ...../ År .....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 -28

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

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑ 1
- Gode ..... ❑ 2
- Vanskelige ..... ❑ 3
- Meget vanskelige ..... ❑ 4

Hvor gamle ble dine foreldre?

- Mor ble ..... 30 _____ år
- Far ble ..... 32 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.	Ja	Nei	Antall
Ektefelle/samboer 34	❑	❑	
Andre personer over 18 år 35	❑	❑	_____
Personer under 18 år 38	❑	❑	_____

Hvilken type bolig bor du i?

- Enebolig/villa ..... 41 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor lenge har du bodd i boligen du bor i nå? ..... 42 _____ år

	Ja	Nei
Er boligen tilpasset til dine behov? 44	❑	❑
Hvis "Nei", er det problemer med:		
Plassen i boligen 45	❑	❑
Ujevn, for høy eller for lav temperatur 46	❑	❑
Trapper 47	❑	❑
Toalett 48	❑	❑
Bad/dusj 49	❑	❑
Vedlikehold 50	❑	❑
Annet (spesifiser) 51	❑	❑
Ønsker du å flytte til en eldrebolig? 52	❑	❑

TIDLIGERE ARBEID OG ØKONOMI

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

- For det meste stillesittende arbeid? ..... 53 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarbeid, husmor, undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har du hatt noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.	Ja	Nei
Sjåfør 54	❑	❑
Bonde/gårdbruker 55	❑	❑
Fisker 56	❑	❑

Hvor gammel var du da du ble pensjonert? ..... 57 _____ år

Hva slags pensjon har du?

- Minstepensjon ..... 59 ❑
- Tilleggspensjon ..... 60 ❑

Hvordan er din økonomi nå?

- Meget god ..... 61 ❑ 1
- God ..... ❑ 2
- Vanskelig ..... ❑ 3
- Meget vanskelig ..... ❑ 4

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?

- Ja, dårligere ..... 62 ❑ 1
- Nei, uforandret ..... ❑ 2
- Ja, bedre ..... ❑ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?

- Mye dårligere ..... 63 ❑ 1
- Litt dårligere ..... ❑ 2
- Omtrent lik ..... ❑ 3
- Litt bedre ..... ❑ 4
- Mye bedre ..... ❑ 5

EGNE SYKDOMMER

Har du noen gang hatt:

Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen. Hvis det har skjedd flere ganger, hvor gammel var du siste gang?

	Ja	Nei	Alder
Lårhalsbrudd 64	❑	❑	_____
Brudd ved håndledd/underarm 67	❑	❑	_____
Nakkesleng (whiplash) 70	❑	❑	_____
Skade som førte til sykehusinnleggelse 73	❑	❑	_____
Sår på magesekken 76	❑	❑	_____
Sår på tolvfingertarmen 79	❑	❑	_____
Magesår-operasjon 82	❑	❑	_____
Operasjon på halsen 85	❑	❑	_____

Har du eller har du hatt:

Sett ett kryss for hvert spørsmål.	Ja	Nei
Kreftsykdom 88	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Parkinsons sykdom	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis 93	❑	❑
Benskjørhet (osteoporose)	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren 98	❑	❑
Gjentatt, ufrivillig urinlekkasje	❑	❑
Grønn stær	❑	❑
Grå stær	❑	❑
Slitasjegikt (artrose)	❑	❑
Leddgikt 103	❑	❑
Nyrestein	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue 108	❑	❑
Matvareallergi	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

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

	Ja	Nei
Har du hatt dette de siste 14 dager? 113	❑	❑

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.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 114	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 120	❑	❑	❑	❑	❑	❑
Kreftsykdom 126	❑	❑	❑	❑	❑	❑
Høyt blodtrykk 132	❑	❑	❑	❑	❑	❑
Astma 138	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 144	❑	❑	❑	❑	❑	❑
Slitasjegikt (artrose) 150	❑	❑	❑	❑	❑	❑
Psykiske plager 156	❑	❑	❑	❑	❑	❑
Alderdomssløvhet 162	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 168	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 174	__	__	__	__	__	

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 184	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 185	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 186	❑	❑
Har du hatt episoder med piping i brystet? 187	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 188	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde 191	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 192	❑	❑
Har du gått ned i vekt siste året? 193	❑	❑
Hvis "Ja":		
Hvor mange kilo? 194	_____ kg	

Hvor ofte er du plaget av søvnløshet?

- Aldri, eller noen få ganger i året ..... 196 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

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

- Ingen spesiell tid ..... 197 ❑ 1
- Særlig i mørketiden ..... ❑ 2
- Særlig i midnattsoltiden ..... ❑ 3
- Særlig vår og høst ..... ❑ 4

	Ja	Nei
Pleier du å ta en lur på dagen? 198	❑	❑
Føler du at du vanligvis får nok søvn?	❑	❑

Er du plaget av:	Nei	Litt	I stor grad
Svimmelhet 200	❑	❑	❑
Dårlig hukommelse	❑	❑	❑
Kraftløshet	❑	❑	❑
Forstoppelse 203	❑	❑	❑

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

- Ikke i det hele tatt ..... 204 ❑
- Bare i liten grad ..... ❑
- En del ..... ❑
- Ganske mye ..... ❑

LEGEMLIGE FUNKSJONER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre?	Ja	Med noe hjelp	Nei
Gå innendørs i samme etasje 205	❑	❑	❑
Gå i trapper	❑	❑	❑
Gå utendørs	❑	❑	❑
Gå ca. 500 meter	❑	❑	❑
Gå på toalettet	❑	❑	❑
Vaske deg på kroppen 210	❑	❑	❑
Bade eller dusje	❑	❑	❑
Kle på og av deg	❑	❑	❑
Legge deg og stå opp	❑	❑	❑
Spise selv	❑	❑	❑
Lage varm mat 215	❑	❑	❑
Gjøre lett husarbeid (f.eks. oppvask)	❑	❑	❑
Gjøre tyngre husarbeid (f.eks. gulvvask)	❑	❑	❑
Gjøre innkjøp	❑	❑	❑
Ta bussen	❑	❑	❑

	Ja	Vanskelig	Nei
Kan du høre vanlig tale (evt. med høreapparat)? 220	❑	❑	❑
Kan du lese (evt. med briller)? 221	❑	❑	❑

Er du avhengig av noen av disse hjelpemidlene?

	Ja	Nei
Stokk 222	❑	❑
Krykke	❑	❑
Gåstol (rullator)	❑	❑
Rullestol	❑	❑
Høreapparat	❑	❑
Trygghetsalarm 227	❑	❑

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært: *Sett 0 hvis du ikke har hatt slik kontakt.*	Antall ganger siste år
Hos vanlig lege/legevakt 228	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 234	_____
Innlagt i sykehus	_____
Hos fysioterapeut	_____
Hos kiropraktor 240	_____
Hos akupunktør	_____
Hos tannlege	_____
Hos fotterapeut 246	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

Har du hjemmehjelp?	Ja	Nei
Privat 252	❑	❑
Kommunal	❑	❑

Har du hjemmesykepleie? ..... ❑ ❑

Er du fornøyd med helse- og hjemmetjenesten i kommunen?	Ja	Nei	Vet ikke
Prinsippet med fast lege 255	❑	❑	❑
Hjemmesykepleien	❑	❑	❑
Hjemmehjelpen	❑	❑	❑

Er du trygg på at du kan få hjelp av helse- og hjemmetjenesten hvis du trenger det?

- Trygg ..... 258 ❑ 1
- Ikke trygg ..... ❑ 2
- Svært utrygg ..... ❑ 3
- Vet ikke ..... ❑ 4

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
Sett 0 hvis du ikke har brukt midlene.

Legemidler

- Smertestillende ..... 259 _____ mnd.
- Sovemedisin ..... _____ mnd.
- Beroligende midler ..... _____ mnd.
- Medisin mot depresjon ..... 265 _____ mnd.
- Allergimedisin ..... _____ mnd.
- Astmamedisin ..... _____ mnd.
- Hjertemedisin (ikke blodtrykksmedisin) ..... 271 _____ mnd.
- Insulin ..... _____ mnd.
- Tabletter mot diabetes (sukkersyke) ..... _____ mnd.
- Tabletter mot lavt stoffskifte (thyroxin) ..... 277 _____ mnd.
- Kortisontabletter ..... _____ mnd.
- Midler mot forstoppelse ..... _____ mnd.

Kosttilskudd

- Jerntabletter ..... 283 _____ mnd.
- Vitamin D-tilskudd ..... _____ mnd.
- Andre vitamintilskudd ..... _____ mnd.
- Kalktabletter eller benmel ..... 289 _____ mnd.
- Tran eller fiskeoljekapsler ..... _____ mnd.

FAMILIE OG VENNER

Har du nær familie som kan gi deg hjelp og støtte når du trenger det? 293	Ja	Nei
	❑	❑

Hvis "Ja": Hvem kan gi deg hjelp?

- Ektefelle/samboer ..... 294 ❑
- Barn ..... ❑
- Andre ..... ❑

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ..297 ____ **gode venner**
Tell ikke med dem du bor sammen med, men ta med andre slektninger!

	Ja	Nei
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, slekt, naboskap, arbeidsplass eller organisasjon)?

- Sterk tilhørighet ..... 300 ❑ 1
- Noe tilhørighet ..... ❑ 2
- Usikkert ..... ❑ 3
- Liten eller ingen tilhørighet ..... ❑ 4

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

- Aldri, eller noen få ganger i året ..... 301 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

KOSTVANER

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 302 _____ Antall

Hvor mange ganger i uken spiser du varm middag? ..... 304 _____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss.

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 306	❑	❑	❑	❑ 310

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

- Meierismør ..... 311 ❑
- Hard margarin ..... ❑
- Bløt (Soft) margarin ..... ❑
- Smør/margarin blanding ..... ❑
- Oljer ..... 315 ❑

Hvor mye (i antall glass, poteter eller brødskiver) spiser/drikker du vanligvis daglig av følgende matvarer?
Kryss av for alle matvarene.

	Ingen	Mindre enn 1	1-2	3 og mer
Melk alle sorter (glass) 316	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑
Poteter	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød) ...	❑	❑	❑	❑
Brødskiver med				
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑
– gulost	❑	❑	❑	❑
– kaviar 322	❑ 1	❑ 2	❑ 3	❑ 4

Hvor mange ganger i uka spiser du vanligvis følgende matvarer?
Kryss av for alle matvarene.

	Aldri	Sjeldnere enn 1	1	2 og mer
Yoghurt 323	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑
Middag med				
– rent kjøtt	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer)	❑	❑	❑	❑
– mager fisk (f.eks. torsk) 328	❑	❑	❑	❑
– grønnsaker (rå eller kokte)	❑	❑	❑	❑
Gulrøtter (rå eller kokte)	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑
Appelsiner, mandariner o.l. 333	❑ 1	❑ 2	❑ 3	❑ 4

TRIVSEL

Hvordan trives du med å bli gammel - alt i alt?

- Godt ..... 334 ❑ 1
- Ganske bra ..... ❑ 2
- Opp og ned ..... ❑ 3
- Dårlig ..... ❑ 4

Hvordan ser du på livet fremover?

- Lyst ..... 335 ❑ 1
- Ikke så verst ..... ❑ 2
- Nokså bekymret ..... ❑ 3
- Mørkt ..... ❑ 4

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 336 _____ år

Hvor gammel var du da menstruasjonen sluttet? ..... 338 _____ år

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent 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.

Barn:	Fødselsår:	Antall måneder med amming:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? ..... 366 Ja ❑ Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 367	❑	❑
Eggehvite i urinen 369	❑	❑

ØSTROGEN-MEDISIN

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

	Nå	Før	Aldri
Tabletter eller plaster 371	❑	❑	❑
Krem eller stikkpiller 372	❑	❑	❑

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

Takk for hjelpen! Husk å postlegge skjemaet idag!
Helseundersøkelsen i Tromsø

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