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Atrial fibrillation in the Tromsø Study 1994-2007

Risk factors, occurrence and gender differences

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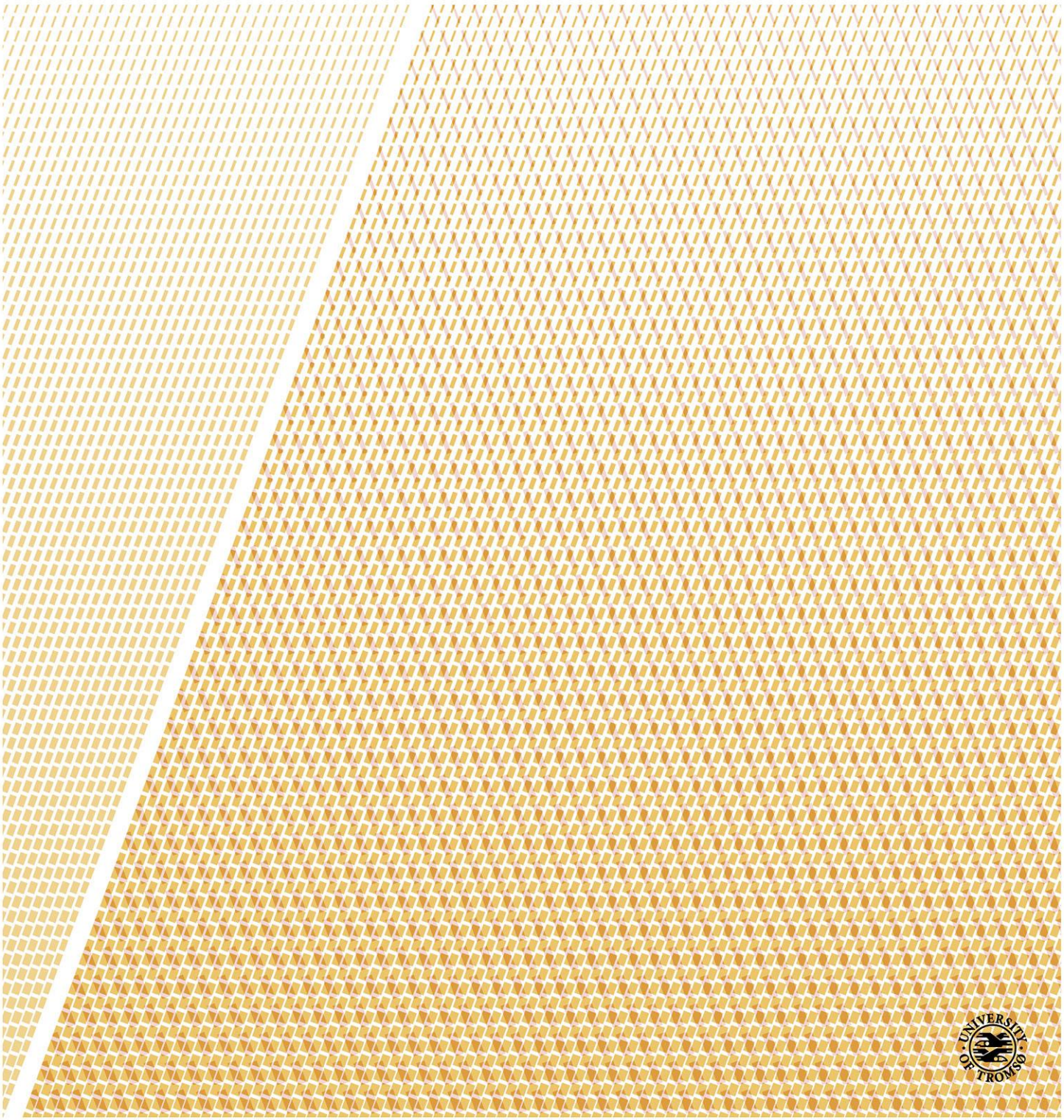
Audhild Nyrnes

A dissertation for the degree of Philosophiae Doctor – Month 20xx



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Tromsø, July 2015

Audhild

The diehard epidemiologist would perform complex statistical adjustments and modelling, but the cynic would argue that mathematical formulae can never fully account for all biological diversity and pathophysiology.

G.Y.Lip, G.I.Varughese, International Journal of Cardiology 2005; 105(3): 319-321

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Age, gender, hypertension, coronary heart disease, obesity, diabetes

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SUMMARY

Atrial fibrillation (AF) is a common cardiac arrhythmia, which increases morbidity and mortality and thereby imposes high health costs on society. The prevalence of AF has increased for several decades, and is expected to increase further, with the rising numbers of elderly people and survivors of heart diseases. Several risk factors for AF related to genetics and diseases have been established. Focus is now also set on novel risk factors related to symptoms, life style and inflammation. The identification of risk factors is important, as some of them could be modifiable.

The population-based Tromsø Study made it possible to follow survey participants from the fourth survey in 1994, who were free of AF at baseline, to study different risk factors for AF and the impact of these. We also wanted to investigate the frequency of AF in our population. All research questions were analysed with a gender perspective.

We were able to follow nearly 23 000 persons for a mean of 11 years, and found that 2.2% of women and 3.3% of men in this population were diagnosed with AF.
A main new finding was the importance of self-reported palpitations as a risk factor for AF. The association was stronger in men than in women. We also found different strength of associations in women and men for several other variables. Coronary heart disease and overweight were stronger risk factors in men. Hypertension was a stronger risk factor in women, and diabetes predicted AF in women only.
A limited number of inflammatory biomarkers were available for this study. We found that hs-CRP was associated with future AF in men, but not in women. Moreover, we found a significant increase in AF with increasing levels of white blood cells.
We also found that serum uric acid was a strong risk factor for AF, and the predictive ability was stronger for women than for men.
Low physical activity, vigorous exercise, smoking and use of alcohol were not associated with AF in this population.

The findings imply that adequate antihypertensive treatment is probably important to prevent AF, as is the prevention of coronary disease and diabetes. Patients with palpitations are prone to AF and should be investigated further. The possible clinical importance of the positive associations with inflammatory biomarkers and uric acid needs further investigation in other populations.

SAMMENDRAG

Atrieflimmer (AF) er en relativt vanlig arytmi, som øker sykelighet og dødelighet, og dermed også samfunnets behandlingsbehov og helsekostnader. Prevalensen av AF har økt gjennom flere tiår, og er forventet å øke ytterligere, på grunn av økende antall eldre i befolkningen, og fordi flere lever lenger med hjertesykdom. Flere risikofaktorer for AF er kjent. Dette gjelder både genetiske disposisjoner, og ulike sykdomstilstander. Det fokuseres nå også på nyere risikofaktorer relatert til symptomer, livsstil og inflammasjon. Kartlegging av risikofaktorer er viktig, fordi noen av disse kan tenkes å være modifiserbare.

Den befolkningsbaserte Tromsøundersøkelsen har gjort det mulig å følge deltakerne fra den fjerde studien i 1994, for å se på ulike risikofaktorer for AF, og hvor stor betydning disse har. Vi ville også undersøke hyppigheten av AF i denne befolkningsgruppen, og om det er forskjeller mellom kjønnene.

Vi fulgte nærmere 23000 personer i gjennomsnittlig 11 år, og fant at 2,2 % av kvinnene og 3,3 % av mennene i vår studiepopulasjon fikk påvist AF. Et nytt hovedfunn i vår studie var betydningen av palpitasjoner. Dette vanlige symptomet som ble rapportert av 27 % av kvinnene og 18 % av mennene, doblet risikoen for AF hos menn og økte risikoen med 60 % hos kvinner. Vi fant også kjønnsforskjeller for flere andre risikofaktorer, der assosiasjonsstyrken var ulik hos menn og kvinner. Koronarsykdom og overvekt var sterkere risikofaktorer hos menn. Hypertensjon var en sterkere risikofaktor hos kvinner, og diabetes predikerte AF bare hos kvinner.
Et begrenset antall inflammatoriske biomarkører var tilgjengelige fra denne undersøkelsen. Vi fant at hs-CRP var assosiert med AF hos menn, men ikke hos kvinner. Det var også økende hyppighet av AF med økende nivå av hvite blodlegemer.
Vi fant videre at serum-urinsyre var en sterk risikofaktor for AF, spesielt for kvinner.
Vi fant ingen assosiasjon mellom lav fysisk aktivitet, hard/intensiv fysisk aktivitet, røyking eller alkohol i denne populasjonen.

Funnene tyder på at adekvat antihypertensiv behandling trolig er viktig for å forebygge AF, likeens vil forebygging av koronarsykdom og diabetes være viktig. Pasienter med palpitasjoner har risiko for å utvikle AF, og bør derfor følges opp. Betydningen av urinsyre og de inflammatoriske biomarkørene bør undersøkes videre i andre populasjoner.

LIST OF PAPERS

1 Nyrnes A, Mathiesen EB, Njølstad I, Wilsgaard T, Løchen ML.

Palpitations are predictive of future atrial fibrillation. An 11-year follow-up of 22,815 men and women: the Tromsø Study.

Eur J Prev Cardiol. 2013 Oct;20(5):729-36. doi: 10.1177/2047487312446562. Epub 2012 May 15.

2 Nyrnes A, Njølstad I, Mathiesen EB, Wilsgaard T, Hansen JB, Skjelbakken T, Jørgensen L, Løchen ML.

Inflammatory biomarkers as risk factors for future atrial fibrillation. An eleven-year follow-up of 6315 men and women: the Tromsø study.

Gend Med. 2012 Dec;9(6):536-547.e2. doi: 10.1016/j.genm.2012.09.001. Epub 2012 Oct 6

3 Nyrnes A, Toft I, Njølstad I, Mathiesen EB, Wilsgaard T, Hansen JB, Løchen ML.

Uric acid is associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women--the Tromso Study.

Europace. 2014 Mar;16(3):320-6. doi: 10.1093/europace/eut260. Epub 2013 Aug 30.

ABBREVIATIONS

ACE-I	Angiontensin-converting enzyme inhibitor
AF	Atrial fibrillation
BP	Blood pressure
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
GFR	Glomerular filtration rate
HDL cholesterol	High density lipoprotein cholesterol
HR	Hazard ratio
hs-CRP	High-sensity C-reactive protein
MI	Myocardial infarction
OPG	Osteoprotegerin
SBP	Systolic blood pressure
SD	Standard deviation
SUA	Serum uric acid
WBC	White blood cells

1. INTRODUCTION/BACKGROUND: Why study atrial fibrillation?

Atrial fibrillation (AF) is the most common disturbance of heart rhythm. The condition confers an increased risk for morbidity and mortality. Despite this, AF has formerly often been regarded as a fairly trivial disorder, and the importance of treatment has been unrecognised. The reason for this neglect can assumedly be related to the lack of knowledge about pathophysiology, risk factors and consequences, as well as missing knowledge and possibilities for good treatment.

AF was described already in ancient Chinese medicine. In Europe, AF was described in the 12th century by Moses Maimonides, a Spanish/Jewish philosopher and physician. The English physician William Harvey described the fibrillation of auricles in animals in 1628. William Withering, another English physician, introduced the treatment with digitalis in 1785. A step further in the approach came with the invention of the stethoscope by René Laënnec in 1816. However, the real investigation and understanding of AF emerged when the electrocardiogram (ECG) was developed (Einthoven 1900) and with the further development of electrophysiology. The British cardiologist Thomas Lewis was the first to record AF with ECG in 1909. Now AF medicine has developed into a high-tech area, as new treatment possibilities have developed, especially with the ablation techniques.

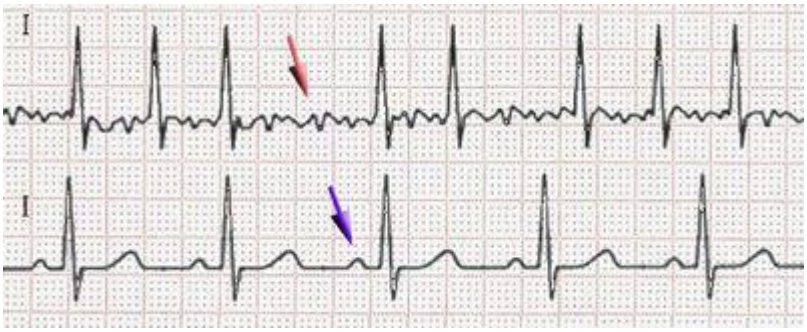
This thesis is an epidemiological study of frequency and risk factors for AF in a general population. Therefore, the diagnosis and management of AF is beyond the scope of the study, and will not be addressed. The mechanisms of pathophysiology will also be addressed very briefly, but needs mentioning due to the link to risk factors.

1.1 What is AF?

AF is an irregular and often rapid heart rate, characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial function. The electrical signals are generated from multiple foci in the atria, typically the areas around the pulmonary veins, instead of following the normal coordinated pathway from the sino-atrial node. This results in a fibrillating atrial activity, which is inefficient and leads to inadequate emptying of the atria. The electrical impulses reaching the atrio-ventricular node will be conducted further to a various degree, and result in irregular contractions of the ventricles, out of coordination with the atrial contractions, and with variable cardiac output. The result is typically poor and irregular blood flow to the body, depending on the amount that has flowed from the atria to the ventricles with each beat.

The diagnosis of AF needs confirmation by an ECG. Distinct P-waves are lacking, and the QRS-complexes will appear “irregularly irregular”.

Figure 1. ECG



Electrocardiogram showing atrial fibrillation (upper lead). P waves are absent and replaced by irregular electrical activity. The ventricular rate is irregular and chaotic. Lower lead: normal. (Illustration: Wikipedia)

1.1.1 Classification

AF has traditionally been classified by its temporal pattern, clinical presentation and response to treatment, and divided in the following groups: (1)

- Paroxysmal: intermittent, self-terminating AF, i.e. spontaneous restoration to normal. Duration may be from less than one hour, up till maximum one week.
- Persistent AF: Duration of one week or more, not self-terminating, often with the need of medical or electrical cardioversion.
- Long-standing persistent AF: refers to persistent AF that has lasted for one year or more.
- Permanent AF: persistent and longstanding AF where restoration to normal rhythm no longer is possible.

A new classification system of AF, based on underlying mechanisms rather than just the symptoms or duration, was proposed by AFNET/EHRA consensus group in 2011. (1) A classification like this could help to better select therapies for specific AF patients.

In addition, the term “lone AF” has generally referred to patients with paroxysmal, persistent, or permanent AF who have no cardiopulmonary disease, hypertension included, and where other precipitating conditions are excluded. The term has primarily been applied to patients younger than 60-65 years of age. As this will only apply to a (small) minority of AF patients, studies on lone AF are scarce and have also rendered inconsistent findings. The risk factors for lone AF may differ from

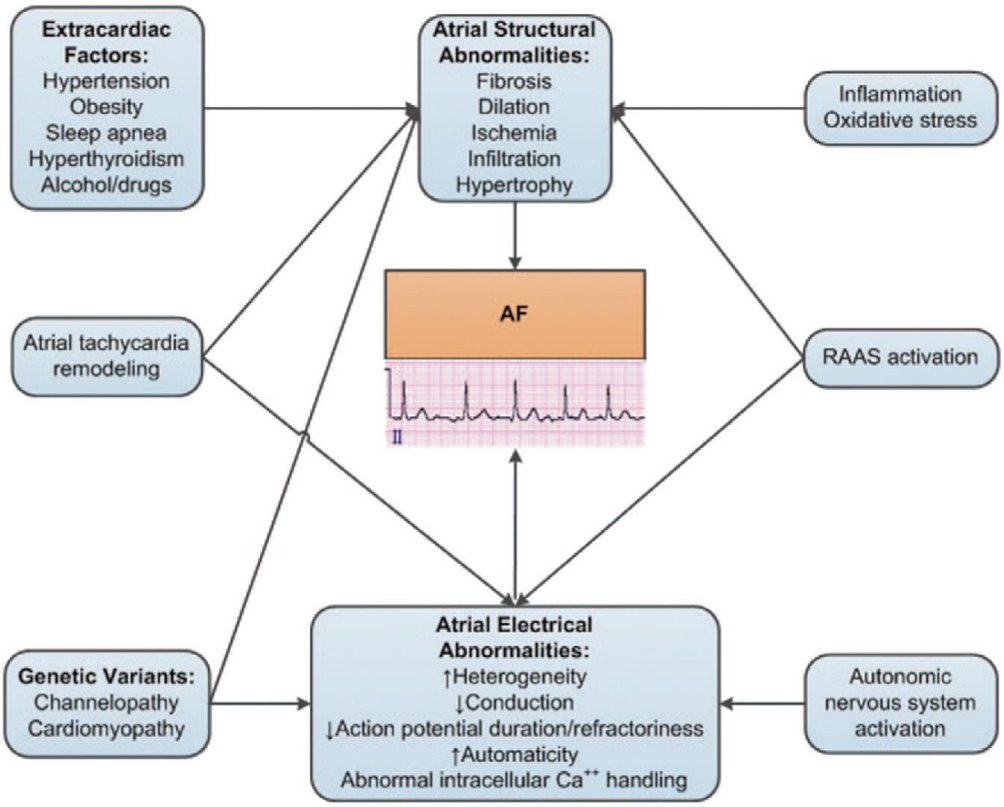
those known to be associated with AF in general. It is possible that lone AF represents a somewhat different condition with other pathophysiological mechanisms.

AF is generally considered a progressive disease, with the tendency to become permanent over time, during which a combination of molecular and structural changes makes it difficult to restore and maintain sinus rhythm.

1.1.2 Pathogenesis/pathophysiology

The pathogenesis of AF is highly complex and is only partly understood. Current evidence indicates multifactorial causes. I will here only briefly mention some aspects of the morphological and electrophysiological alterations that may promote AF.

Figure 2. Mechanisms of AF



2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, JACC Dec 2, 2014

AF indicates atrial fibrillation; Ca^{++}, ionized calcium; and RAAS, renin-angiotensin-aldosterone system.
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AF is a result of “electric chaos” in the atria. This appears to require both an initiating event (trigger) and a permissive atrial substrate. Focal ectopic activity and multiple wavelets have been shown as such triggers. This causes *electrical remodelling*, which can be demonstrated within minutes after onset. The electrical remodelling alters ion channel function. The atrial refractory period is shortened and rate adaptation is lost. This may lead to re-entrant circuits. (2, 3)

Structural remodelling may precede the onset of AF, as in cases of present cardiac disease and atrial dilatation, or may be a result of persisting electric changes. The most frequent structural changes are atrial fibrosis and loss of atrial muscle mass. Fibroblasts can couple electrically to cardiomyocytes and promote reentry and/or ectopic activity. Inflammatory changes have been demonstrated in atrial biopsies, and inflammation appears to contribute to the structural changes in AF, as does oxidative stress. (2, 3)

Autonomic nervous system factors are also important in AF. *Autonomic neural remodelling* contributes to positive feedback loops that promote AF persistence and recurrence. (4) The clinical forms, and the evolution from paroxysmal to persistent to permanent AF, are considered to reflect the progressing electric and structural changes in the atria.

Risk factors associated with future AF may influence the substrate, and possibly also the triggers, for AF onset and persistence.

1.2 Clinical implications of AF

A 2012 consensus statement described AF as one of the major common and chronic disorders in modern cardiology, adding that mortality and morbidity associated with AF "remain unacceptably high". (1)

Symptoms of AF may vary, from lacking or negligible, to serious. Common symptoms include palpitations, fatigue, lightheadedness, dyspnea on exertion, and initiation or aggravation of angina, causing reduced quality of life and the need of health care.

The most serious complication of AF is arterial thromboembolism. Many factors have been shown to contribute to this. Due to altered and deteriorated contractility with insufficient emptying of the atria, blood stasis and atrial clot formation can occur. In addition, abnormal changes in blood constituents have been described, including haemostatic and platelet activation. Moreover, inflammation is likely to contribute. (5)

The most clinically evident thromboembolic event is ischemic stroke. AF increases the stroke risk up to five times. (6, 7) AF is present in 15-30% of patients with acute stroke and is associated with a 1.5- to 3.0-fold higher mortality compared to stroke patients in sinus rhythm. Strokes attributed to AF also tend to be more severe, resulting in greater disability, longer hospital stay, and lower rate of patient discharge to own home. (6, 8, 9)

Paroxysmal AF have been thought to imply the same stroke risk as persistent or permanent AF, as indicated in a Swedish study from 2010. (10) However, other trials have reported higher stroke risk in patients with permanent compared to paroxysmal AF. This was also concluded in two studies published lately, (11, 12) also in patients receiving anticoagulation.

Moreover, AF has been shown in a number of studies to be associated with impaired cognitive function, also in subjects without a history of stroke. (13-16)

AF is associated with a tripled risk for heart failure, and a doubling of the overall mortality risk. (17-19)

AF also seems to be a risk factor for incident myocardial infarction (MI). A recent US study found that subjects with AF had a 2-fold increased risk for MI, which remained significant after adjustment for known risk factors for coronary heart disease and the use of warfarin, and with a stronger association in women. (20)

AF patients need hospitalization twice as often as those without AF, when adjusted for comorbidities. (19, 21) Hence, hospitalizations attributable to AF represent a substantial and increasing economic challenge in many countries.

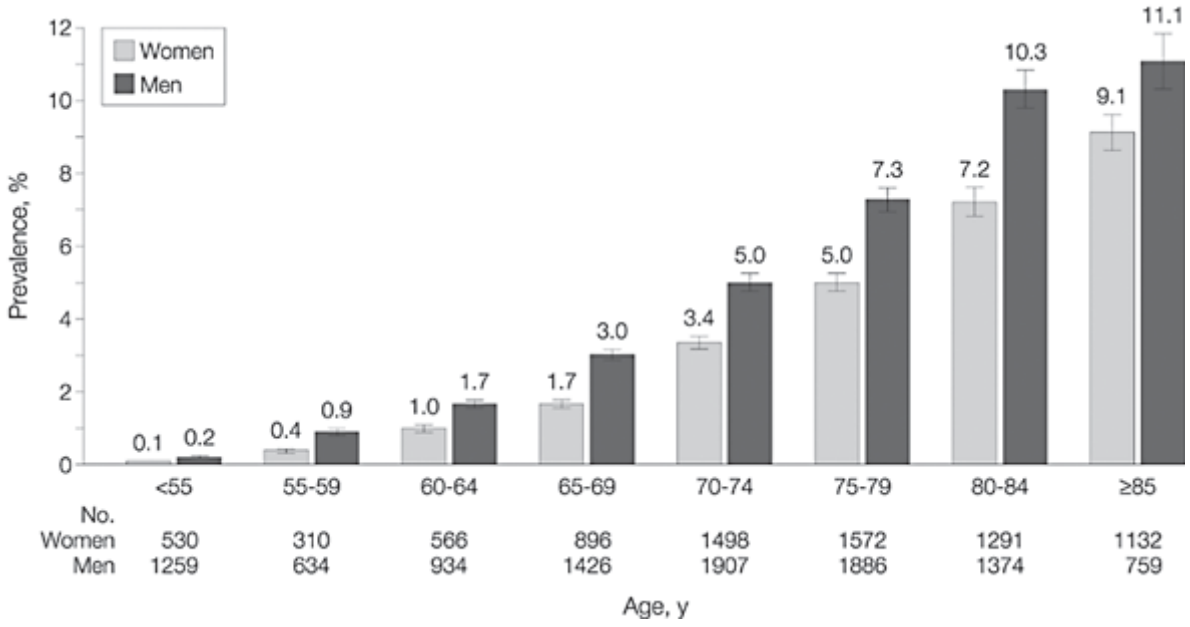
Due to the high prevalence of AF, this condition represents a large health burden with high costs for society. All indicators point to an increasing burden of AF in the 21st century. Estimates vary, due to different methodologies, but all investigators agree that an increase is indisputable, and that a 2.5 fold increase in prevalence is a cautious estimate. (22-24) Hence, it is important to investigate possible strategies to limit and preferably prevent the development of AF. The identification of risk factors serves the purpose of pinning down potentially modifiable factors, with the hope of reducing health problems.

1.3 Epidemiology of AF

1.3.1 Prevalence

The overall prevalence of AF has previously been estimated to 1-2% in the general population, and has been found to double with each decade from the age of 50 years to a prevalence of approximately 10% in those aged 80 years or more. (22, 25) The condition is uncommon, but not absent, in younger persons. Estimates of prevalence are highly dependent on the methods used for identification and ascertainment of AF. As many cases of AF are silent and/or paroxysmal, these are easily missed in studies. (See also chapter 6.2, paragraph re. information bias and misclassification.)

Figure 3. Prevalence of atrial fibrillation with age. The ATRIA Study



Data from Go AS, Hylek EM, Phillips K, et al. JAMA 2001; 285:2370. (ATRIA study)

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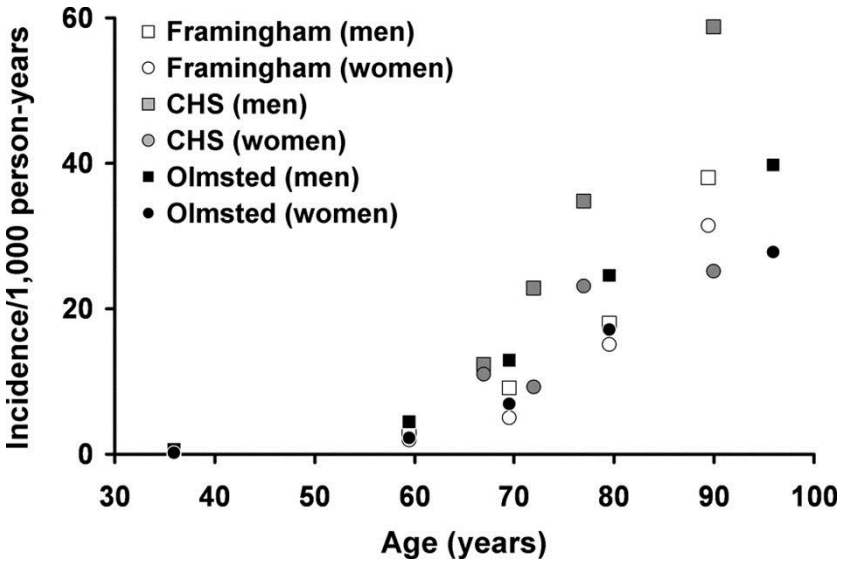
The prevalence of AF is lower among black African/Caribbean and South Asian ethnic groups than in the white population. (26, 27) This is despite some common risk factors, e.g. hypertension and diabetes, being more prevalent among these groups. These consistent ethnic differences in prevalence and outcome are unlikely to be due to differential ascertainment. (27) White patients also have a higher risk of postoperative AF than black and other non-Caucasian patients. (28)

A review by Ball and co-workers 2013 presents pooled analyses of population data, suggesting that the overall prevalence in the adult population is more likely between 2.5% and 3.5%. (24)

1.3.2 Incidence

Studies of incidence of AF have yielded varying numbers, due to heterogeneity of the populations studied, and the prevalence and type of concomitant diseases, especially cardiovascular diseases. Incidence numbers from published data are therefore difficult to compare. All studies have demonstrated that AF incidence increases with age, and is higher in men than in women. Three of the most cited American population studies, published between 1994 and 2006, are compared in figure 4.

Figure 4. Incidence of AF per 1000 person-years stratified by age in the Framingham Heart Study, the Cardiovascular Health Study (CHS), and the Olmsted County Study.



Miyasaka Y et al. Circulation 2006;114:119-125

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In Europe, incidence in the Rotterdam Study (published 2006) was similar to the data from North America. A recent, large study from Germany found higher incidences than previous studies, especially in the age groups above 70 years. (29)

Population studies performed in the 1980s and 1990s indicated an increasing incidence over time. However, newer data from US have shown stable incidence rates. This applies to the ARIC Study 1987-2004, (26) among Medicare beneficiaries 1993-2007 (30) and also recent data from Olmsted county 2000-2010. (31)

1.3.3 Increasing numbers

Population studies have consistently indicated increasing prevalence, and until lately also increasing incidence. (23, 24, 32, 33) The reason for this increase is partly due to ageing populations, surviving with more comorbidities predisposing for AF. In addition, the increasing focus on AF, as well as improved diagnostic tools, has led to the detection of a larger proportion of AF patients. The impact of risk factors may also have changed. As an example of such, obesity and diabetes, both of which are associated with AF, have increased in the population.

A recent report from the Framingham Heart Study presents 50-year trends in prevalence and incidence of AF. In the sex-stratified and age-adjusted analysis of more than 200 000 person-years, both prevalence and incidence showed a roughly four-times increase, somewhat lower for women. However, the incidence of AF by Framingham Heart Study ECGs did not change significantly over time, and the researchers conclude that the trends of increased prevalence and incidence of AF partly are due to enhanced detection. (34)

1.3.4 Gender differences

At all ages, the prevalence and incidence of AF is higher in men than in women, across all studies and in all age groups. (24) The reason for this gender difference remains unknown. In the older age groups (80+), more patients are female, due to the age composition in the population, with more women surviving to old age. Patients in the youngest age groups are predominantly men. Women tend to be on average 5 years older than men when they are first diagnosed with AF. (35, 36) This could in part be related to concomitant diseases; especially coronary heart disease (CHD) which is a strong risk factor for AF and which also has a later onset in women. Still, the gender differences in prevalence and incidence remain after adjustment for such comorbidities.

At time of AF presentation, men more often have CHD and more heart failure with reduced systolic function. Women have more hypertension, heart failure with preserved systolic function, valvular disease, and diabetes. (35-37)

Many studies have found that risk factors for AF are differently distributed in women and men, and also that the risk factors show various strength of association in the two genders. However, these differences are not consistent throughout the studies. This could be explained by differences in the populations studied, and that adjustment for confounders has been done differently.

2. RISK FACTORS

Risk factors are usually addressed under the heading “epidemiology”. However, as this thesis entirely focuses on risk factors, I have chosen to present these in a separate chapter.

A risk factor is a characteristic or exposure, associated with an increased risk of a condition or disease. Risk factors may be biomedical, behavioural, environmental, demographic or genetic. Risk factors are correlational, but not necessarily causal. They do not prove causation, but can be part of the causal chain. The identification of risk factors is important, as some of these may be modifiable. A modification of risk factors may help reduce health problems.

2.1 Genetic factors

The knowledge in this field is rapidly changing and increasing, and will therefore be mentioned very briefly here.

Genetic factors have been assumed to play a role in AF, as the condition can be observed to affect several members of certain families. A genetic disposition may particularly be of importance in cases of lone AF, which affects otherwise healthy individuals. (38-40) Over the past decade, genome-wide association studies (GWAS) have led to the identification of multiple gene variants that confer increased susceptibility to the arrhythmia. These genes encode ion channels, transcription factors, and signalling molecules. (41) The Tromsø Study has also contributed in the genetic analyses, in cooperation with Icelandic researchers who showed a 21% increased risk for AF in the presence of a certain gene variant. (42)

The heritability of AF is complex. For the majority of patients, a possible genetic susceptibility is probably a polygenic phenomenon, meaning that it is due to the combined effects of a number of genes, in addition to the effect of other risk factors.

2.2 Cardiovascular, life style related and other risk factors

2.2.1 Cardiovascular risk factors

The most studied risk factors for AF are those related to cardiovascular disease (CVD). These factors have been studied in large, and more selected, populations in many countries.

Hypertension has consistently been found to be one of most important risk factors. (18, 37, 43) Although the increase in risk is relatively modest (relative risk 1.2-1.5), (7) hypertension is considered the most significant population-attributable risk factor for AF, due to the high prevalence in the general population. Hypertension is associated with structural changes in the heart, related to left atrial enlargement and left ventricle hypertrophy. (44) The electrical remodelling occurs early in hypertensive heart disease. (45) This can lead to atrial and ventricular arrhythmias. The activation of the renin-angiotensin-aldosteron system is important in hypertension, and also in the development of atrial fibrosis which is correlated to AF. (46-48)

CHD, valvular disease and congestive heart failure (CHF) are well known risk factors for AF. (17, 24, 37, 43, 49)
In the Framingham Study, CHF imposed the greatest risk, with a 4.5-fold increase risk for AF in men and a 5.9-fold increased risk in women. (7) CHF may, among others, be the result of hypertension, valvular disease, CHD or even tachy-arrhythmias like AF, but is a risk factor for AF even when adjusted for these comorbidities.
Valve disease appears to be a stronger risk factor for AF in women. In the Framingham Study, the OR was 3.4 in women and 1.8 in men, in risk factor adjusted analysis. (37)
CHD is a stronger risk factor in men. In Framingham, the odds ratio for AF was 1.4 in men with previous myocardial infarction, while the association in women was not significant. (37) Other large population studies have not given information on sex-specific analyses. However, in most reports men are more likely to show ECG evidence of past myocardial infarction.

2.2.2 Life style related risk factors

Life style factors have shown an association in some studies, while others have failed to establish a correlation.

Smoking was shown to increase the risk for AF in the Rotterdam Study (50) and also in the ARIC Study, (51) while other large population studies (Cardiovascular Health Study, Renfrew/Paisley Study, Copenhagen City Heart Study, Danish Diet Cancer and Health Study) found no significant association.

Alcohol in light to moderate amounts appears to be associated with a lower risk of CVD and also with all-cause mortality. Heavier use, as well as abstention, is associated with a higher risk. The effects on AF are less clear, as studies have been diverging. Episodic high alcohol consumption as a trigger of arrhythmias, AF included, has been recognised since 1978 (52) and is termed the “holiday heart syndrome”. Several epidemiological studies have found that habitually high alcohol consumption is

associated with incident AF. (53-55) A meta-analysis 2011 concluded that the risk of developing AF is increased with increasing levels of alcohol intake, while the effect of light drinking remains uncertain. (56)

Coffee has been reported by some patients to trigger paroxysms of AF. However, larger studies have found no significant association. (57-59)

Poly-unsaturated fatty acids (PUFAs) have been hypothesized to have anti-inflammatory and anti-arrhythmic effects and to protect against AF. Studies in this field have yielded mixed and mostly disappointing results. A meta-analysis of seven cohort studies and 11 randomized controlled trials, published 2012, showed no significant reduction of incident AF with PUFA-exposure. (60) Several studies assessing PUFAs for the prevention of post-operative AF and post-ablation recurrence of AF have also showed no significant effect, as summarized in a meta-analysis 2013. (61)

Physical activity has been much focussed in later years, as long-time vigorous exercise (typically marathon and similar activities) has been shown in several studies, both clinical and meta-analyses, to increase the risk for AF. (62-65) Light to moderate physical activity has shown no increased risk, and could also have a protective effect, according to the same analyses. A favourable effect could partly be mediated via positive effects on cardiovascular risk factors.

2.2.3 Other life-style related and non-cardiac risk factors

Hyperthyroidism is a well-known risk factor for AF. Other conditions that have come into attention in recent years include obstructive sleep apnea, chronic kidney disease, chronic inflammatory disease, and surgery, especially cardiac.

Obesity has been investigated in a number of studies of various designs, and has consistently been found to increase the risk for incident AF. (66-69)
Diabetes has also shown an association in most studies. (37, 49, 70)
Obesity and diabetes frequently co-exist, along with hypertension, obstructive sleep apnea, CVD, chronic kidney diseas and inflammatory states, all of which are also correlated with AF.

2.3 Palpitations

Palpitations are a sensory symptom, an awareness of the beating of the heart, which may be felt as rapid, irregular or forceful and often is perceived as unpleasant.

The biological mechanism for this is not elucidated, which is also stated in the position paper from the European Heart Rhythm Association in 2011, Management of patients with palpitations: "Little is known about the events responsible for heartbeat sensation, the afferent sensory pathways that are involved, or the higher-order cognitive processing that filters, modulates, and amplifies these stimuli and brings some to conscious attention." (71) Palpitations can be a benign sensation, or indicate a dangerous arrhythmia. Studies concerning the frequencies of significant arrhythmias in persons reporting palpitations have yielded highly varying results, depending on the population studied.

Two previous publications from the Tromsø Study have addressed the phenomenon of palpitations, but found a poor relationship between perceived palpitations and recorded arrhythmias, as assessed by 24-h ambulatory ECG in a population sample. (72, 73) The importance of self-reported palpitations on later occurrence of AF has not been documented until now.

2.4 Biomarkers in AF

A biomarker (biological marker) is a substance that can be objectively measured and used as an indicator of a biological state such as a disease or condition. In a wider definition, a biomarker can also be a biologic feature, characteristic or process. Biomarkers have been widely studied in medical research and in clinical medicine, and are increasingly used in the assessment of present and future disease. In AF research, a large number of biomarkers have been studied and have shown an association with AF, however conflicting. Whether an associated biomarker has a causal relationship to this condition, or is a confounder or merely a bystander, often remains a highly challenging problem. With further research, biomarkers associated with future AF can hopefully be used to improve clinical risk assessment. Moreover, they could also improve the understanding of the pathophysiology, and eventually point to new treatment possibilities.

2.4.1 Inflammatory markers

The correlation between inflammation and cardiovascular disease has been recognised through several decades. However, a causal relationship is still debated. The role of inflammation in AF pathogenesis was first reported in 1997, when histologic changes consistent with myocarditis in atrial tissue were demonstrated in patients with AF. (74) Inflammation has later been shown in several studies to be associated with AF, although results are inconsistent. However, the majority of studies

report elevated levels of inflammatory markers in AF compared with controls. To which extent the inflammation is causal is still being debated, but the inflammatory process seems to have importance both for the development and perpetuation of AF. (75) Studies have also indicated a correlation between inflammatory markers and the AF burden. (76)

Four inflammatory biomarkers were available for the analyses in this thesis: high-sensitivity CRP (hs-CRP), osteoprotegerin (OPG), white blood cells (WBC) and fibrinogen.

The most studied inflammatory biomarker is C-reactive protein (CRP), considered to reflect underlying disease processes associated with AF. Special attention has been paid to hs-CRP, as a marker of low-grade inflammation, which has proven to be a risk factor for cardiovascular disease in general, and also for AF in some studies. (76, 77)

OPG is a novel biomarker that has gained interest as a marker of CVD. OPG is associated with inflammation, vascular calcification, endothelial function and atherosclerosis. A recent study from Tromsø showed that high plasma OPG is a strong predictor of CVD and mortality, in high risk and general populations. (78) As far as we know, only one previous study has addressed a potential correlation between OPG and AF. This is a report from the Framingham Offspring Cohort published 2009, where OPG no longer was associated with AF after adjustment for MI and heart failure. (79)

The level of WBC as a marker of future AF in a general population has, to our knowledge, not been investigated previously.

Fibrinogen has been studied with conflicting results regarding the prediction of AF. Some population studies have found that fibrinogen predicted future AF, (77, 80, 81) while others did not find such a correlation. (79, 82, 83)

2.4.2 Uric acid

Uric acid (UA) is an “old” substance that has gained new attention. Apart from its ability to cause gout and stone formation, UA was for many years thought merely to be the metabolically inert waste product of purine metabolism. However, the last decades have provided increasing evidence that this substance is biologically active, and is involved in many biological functions.

UA is the breakdown product of purine catabolism. UA is excreted in the kidneys, but approximately 90% of filtered UA is reabsorbed. The reason for this reabsorption is not fully understood, as high

levels of UA have been shown to be unfavourable in many aspects. However, it is reasonable to assume that UA has also had beneficial effects through evolution and physiology.

Increased serum UA levels have been found to be associated with hypertension, inflammation, CVD, obesity, endothelial dysfunction, renal disease and diabetes. All these conditions are also associated with AF. UA has especially been studied as a marker of CVD and a measure of CVD risk factor load. Increased UA levels were independently and significantly associated with risk of cardiovascular mortality in the NHANES study. (84) In a Finnish population-based prospective cohort study, UA levels were a strong predictor of cardiovascular disease mortality in healthy middle-aged men, independent of variables commonly associated with gout or the metabolic syndrome. (85) In a large Austrian cohort of elderly women, UA was an independent predictor for all major forms of death from CVD, CHF and stroke. (86) A recent publication from the Tromsø Study also confirmed that UA is a risk factor for ischemic stroke and all-cause mortality in a general population. (87)

UA has shown to have strong antioxidant activity, and also seems to have protective effects against neurodegenerative diseases like Parkinson's disease and multiple sclerosis, (88-90) and also motor neuron disease (ALS). (91) Some of these studies have shown a gender difference, as the favourable effect was seen predominantly in men. The relation between uric acid and cognitive decline, in which both vascular mechanisms and oxidative stress are thought to play a role, has been studied with somewhat conflicting results. In a publication from the Rotterdam Study 2009, higher UA levels were associated with a decreased risk of dementia, after adjustment for cardiovascular risk factors. (92) By contrast, hyperuricaemia was related to white matter atrophy and worse cognition in another publication from the Rotterdam Study 2013. (93) However, some new, large, population based cohort studies have shown that patients with gout have a lower risk of developing dementia, supporting the purported potential neuroprotective role of uric acid. (94, 95)

UA levels in men are higher than in women throughout life, although rising after menopause. Women have a lower risk for gout than men do at comparable uric acid levels, according to 52-year follow-up data from the Framingham Heart Study. (96) However, several studies have found that the effect of UA seems more detrimental in women. This has been shown for cardiovascular risk, (97-99) mortality (84) and diabetes. (98, 100) However, most studies did not perform sex-specific analyses.

An association between UA and AF has been indicated in a few studies. (101-103) This association could partly be mediated through CVD and hypertension, but multivariable analyses have indicated that an independent effect is also possible.

3. AIMS OF THESIS

The overall aim was to identify and investigate occurrence and risk factors for future AF in a longitudinal study of a large general population. All analyses were performed in sex-specific models.

The specific aims were the following:

1. to study prevalence, incidence and traditional risk factors for AF, and especially to investigate the effect of palpitations in prediction of incident AF
2. to study the association between inflammatory biomarkers hs-CRP, OPG, WBC and fibrinogen and future AF
3. to study the association between uric acid and future AF

4. STUDY POPULATION AND METHODS

4.1 The Tromsø Study

The Tromsø Study is a single centre longitudinal study of the population in the municipality of Tromsø, Norway. The study was initiated in 1974, with the main focus on determinants and distribution of cardiovascular diseases, and how to prevent these. Cardiovascular mortality was high in Norway at that time, and even higher in Northern Norway than in the nation as a whole.

The Tromsø Study is also a longitudinal study, as the surveys have been repeated at regular intervals. In addition, the study has gradually expanded to include a variety of diseases and health aspects. The design ensures the inclusion of total birth cohorts and random samples, and involves a large proportion of the adult population. High-risk individuals have been invited to sub-studies.

The sixth Tromsø survey was performed in 2007-08. At this point, a total of 40 051 persons had participated in at least one of the six surveys, while 15 157 had participated on three or more occasions, and 1235 persons had participated in all six studies. The seventh Tromsø survey is scheduled to 2015-16, with the invitation of 33 000 persons. The Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health have approved the surveys.

A letter enclosing a questionnaire, which they are asked to answer and bring to the examination site, invites all participants in the Tromsø Study. Here, the participants are handed a second questionnaire, where they are asked to give supplementary information. The two questionnaires have expanded over the years, and now contain information about a wide range of diseases and symptoms, medication, lifestyle aspects including dietary habits, smoking and physical activity, socio-economic status and ethnicity.

The physical examination consisted originally of the measurements of blood pressure, height and weight, and a blood sample for the analysis of haemoglobin and blood lipids. In later surveys, the physical examination has gradually been extended, as have the blood tests (104)(+ see appendix: questionnaires)

Blood samples for later analyses of novel biomarkers have been stored at each survey. Examples of such biomarkers that have been measured in stored samples include hs-CRP and OPG from the second visit of the fourth survey of the Tromsø Study (Tromsø 4).

4.2 Tromsø 4 cohort

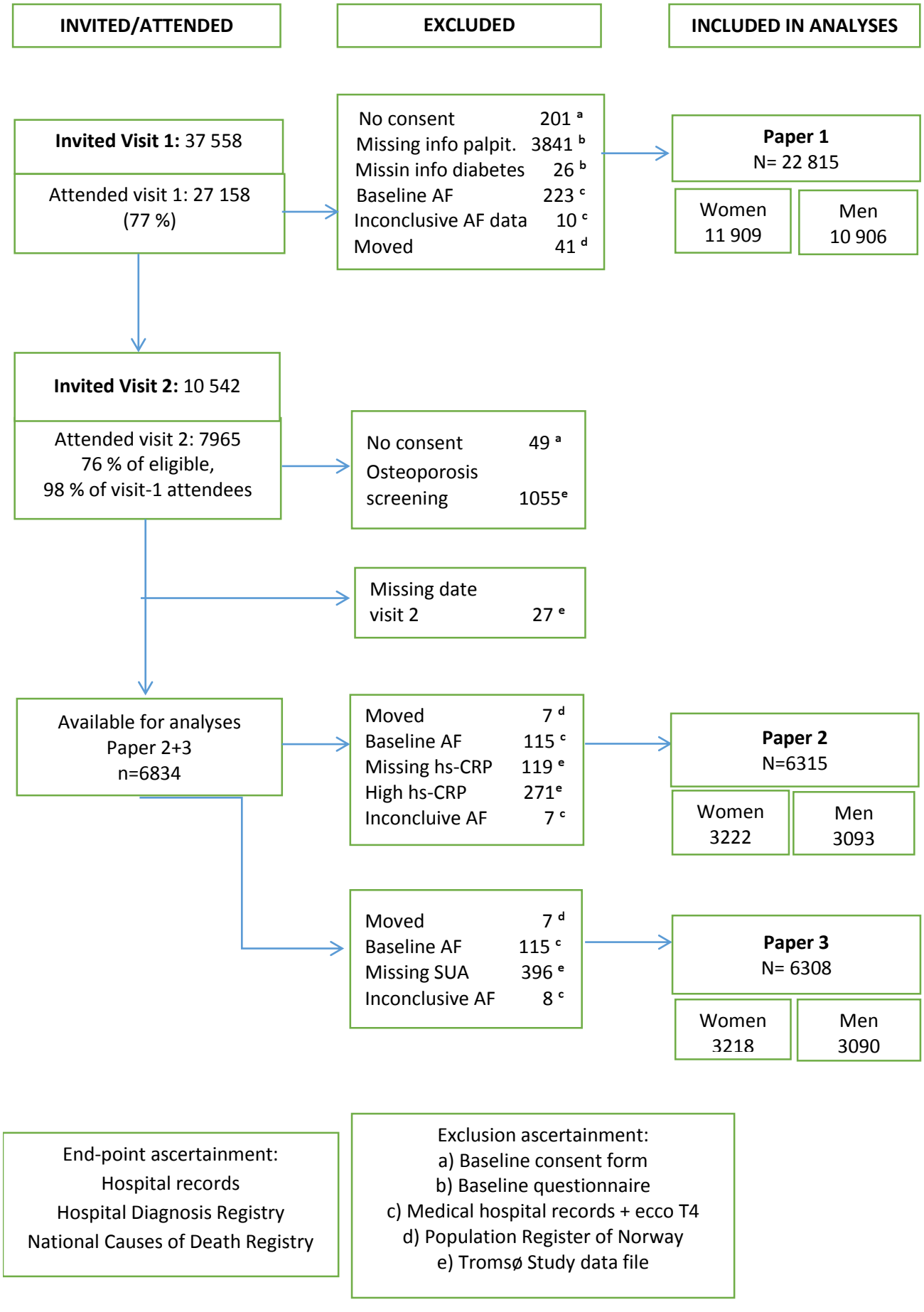
The three papers in this thesis are all based on data from Tromsø 4 in 1994-95.

An overview of the study population is given in the flowchart (figure 5).

In Tromsø 4, all inhabitants 25 years and older (born 1897-1969) were invited. A total of 27 158 persons, 77 % of the eligible population, participated in the first visit of the survey. This group constitutes the study population in paper 1. After exclusions of persons who did not consent to research, those who had moved from the region, persons with known AF at baseline or insufficient data regarding AF, and persons with missing information on palpitations and diabetes, 22 185 persons were followed-up for eleven years.

A pre-defined selection of the participants was invited to a more extensive examination in a second visit, usually within 1-3 months after the first visit. The eligible subjects were identified before attending the first visit. The second visit comprised more specialized physical and biochemical testing. Eligible for the second visit were all men aged 55-74 years (born 1920-39) and all women aged 50-74 years (born 1920-44), as well as 5-8 % random samples of the other age groups (25-54 years and 75-85 years). Of those invited to the second visit, 98 % attended (76 % of the 10 542 originally eligible subjects).

Figure 5. Flowchart, the Tromsø Study, 1994-2007



A total of 7965 persons attended the second visit. This group constitutes the basis for the study population in paper 2 and 3. Of the second visit attendees, 1055 were mainly screened for osteoporosis. This group was not part of the pre-defined second visit population, but was invited in a special project. The group consisted of younger women with a mean age of 49.9 years. Due to the highly selected age, and one gender only, we decided to exclude this group from our analyses. Forty-nine persons had withdrawn their consent to research and were consequently excluded.

In my data set, the selection variable 'date for examination in visit 2' provided 6834 subjects available for further analyses. After exclusions of persons who had moved from the region, persons with known AF at baseline or insufficient data regarding AF, and persons with missing data or high levels of hs-CRP (>10 mg/L), 6315 subjects were followed-up for eleven years in the study of inflammation (paper 2). In the study of uric acid, we did the same exclusions of persons who had moved from the region and persons with known AF at baseline or insufficient data regarding AF, as well as persons with missing uric acid measurements. This provided 6308 subjects with equally long follow-up in the study of uric acid (paper 3).

The populations in visit 1 and 2 thus differ in age, with a mean of 46 and 60 years respectively. The differences in other variables (e.g. blood pressure, BMI, blood lipids, diabetes, and antihypertensive treatment) can mostly be explained by the age difference.

Table 1. Baseline characteristics of participants in Tromsø 4, visit 1 and 2

	Women		**Men**	
	Visit 1	Visit 2	Visit 1	Visit 2
Age, years	45.8 (14.8)	60.5 (10.3)	46.2 (14.1)	59.5 (10.0)
Systolic blood pressure, mmHg	131.0 (21.6)	144.7 (24.3)	137.2 (17.0)	144.6 (20.3)
Diastolic blood pressure, mmHg	75.8 (12.4)	81.7 (13.4)	79.8 (11.6)	84.8 (12.1)
Heart rate, beats/min	73.0 (12.2)	73.9 (12.5)	68.8 (12.5)	69.8 (13.0)
Height, cm	163.9 (6.6)	161.5 (6.3)	177.2 (7.0)	175.2 (6.8)
Body mass index, kg/m²	24.7 (4.1)	25.9 (4.4)	25.6 (3.3)	26.0 (3.3)
Total cholesterol, mmol/L	5.99 (1.37)	6.93 (1.34)	6.04 (1.21)	6.57 (1.20)
HDL-cholesterol, mmol/L	1.65 (0.41)	1.68 (0.43)	1.35 (0.35)	1.39 (0.39)
Alcohol, glass/14 d	3.3 (4.2)	2.5 (3.6)	6.6 (7.6)	5.5 (7.3)
Tee-totaller (%)	14.6	26.1	8.2	12.9
Smoking (%)	36.3	31.0	36.5	34.7
Physical activity (%)	45.6	28.2	60.7	47.1
Hypertension (%)	28.4	56.7	40.4	60.6
Anti-hypertensive treatment (%)	5.4	13.1	5.7	12.8
Coronary heart disease (%)	3.4	8.3	6.2	15.0
Diabetes (%)	1.8	3.9	2.1	4.4

4.3 Data collection and ascertainment of endpoints

Baseline characteristics were collected from the questionnaires, the physical examination and the blood analyses.
From the questionnaires, we selected information about self-perceived arrhythmia ('Have you noticed sudden changes in your heart rate or heart rhythm in the past year?'), and self-reported information on diabetes, angina, myocardial infarction, physical activity, smoking habits, coffee, alcohol and use of antihypertensive treatment.
Height, weight, blood pressure and heart rate were measured at the examination.
Blood tests from the first visit provided full haematological indices and blood lipids (total cholesterol, HDL-cholesterol and triglycerides).
Blood tests from the second visit also included hormones and a number of other substances, among which some inflammatory biomarkers and uric acid have been of special interest for this thesis.
The second visit questionnaire also provided information on anti-diabetic medication. This was incorporated in the definition of diabetes for the analyses in paper 3. ECGs were collected for a subgroup, but these were not available for our analyses.

All cases of AF have been verified in hospital records and validated by a physician.

The procedure for identification, definition and ascertainment of atrial fibrillation is described in detail in the papers. We searched for information on AF in the hospital records of all patients with a diagnostic code (International Classification of Diseases) of AF or other relevant arrhythmia. Moreover, we performed systematic searches among subjects without an AF diagnosis, but who could be assumed to have an increased risk for AF. These were persons with other cardiovascular and cerebrovascular conditions, as well as 'instantaneous inexplained death' and 'death by unknown cause'.

4.4 Statistical analyses

All analyses were performed using SPSS for Windows. Version 15.0 was used for the analyses in paper 1, while the analyses for papers 2 and 3 were performed using version 19.0. Baseline characteristics are presented as means (standard deviation) or numbers (percent). Differences between groups were assessed by t-tests and χ^2 tests. Linear trends across quartiles of measured biomarkers were tested using linear regression models for continuous variables and logistic regression for binary variables. Age-adjusted and multivariable Cox proportional hazards regression

models were used to estimate hazard ratios (HRs) for AF with 95 % confidence intervals. The analyses were conducted separately for women, men and the total study population. Cross-product terms between sex and biomarker variables were added to the models to assess interaction. The proportional hazard assumption was assessed by visual inspection of log minus log plots of the survival curves. A two-sided p-value <0.05 was considered statistically significant.

5. RESULTS

Paper 1: Palpitations are predictive of future atrial fibrillation

This is a study of the total Tromsø 4 cohort, where we analysed 22 815 persons who were followed-up for eleven years. In this large, general population with a mean age of 46 years at baseline, 3.0% of women and 4.2% of men developed AF during follow-up.

We found that hypertension was a significant risk factor for AF. Raised blood pressure at baseline (above 140/90 mmHg) almost doubled the risk of AF in women (HR 1.98, 95% CI 1.46-2.69) and increased the risk by 40% (HR 1.40, CI 1.13-1.74) in men.
We found that self-reported diabetes was a significant risk factor for AF in women.
We could confirm that CHD is a strong risk factor, especially for men. We also found a clear gender difference in the impact of overweight, which was a stronger risk factor for men.

However, our main finding in this study was the importance of self-reported palpitations. Palpitations reported at baseline increased the risk of AF in women by 62% (HR 1.62, CI 1.29-2.02) and in men by 91% (HR 1.91, CI 1.54-2.35).

A low percentage was found to have lone AF, as this applied to only 4.4% of the female and 7.2% of the male AF patients. In our study population, 67% of lone AF patients were men. We found a significant relation between BMI and lone AF in men. We also found that height was a risk factor for lone AF in men. Women with lone AF seemed to be taller and leaner than AF women in general, but due to a low number in this group (n=16), these differences were not significant.

Paper 2: Inflammatory biomarkers as risk factors for future atrial fibrillation

In Tromsø 4, a full blood cell count (including subgroups of white blood cells, WBC) was collected of all participants. In visit 2, new blood samples were collected for the analysis of fibrinogen, high-sensitivity C-reactive protein (hs-CRP) and osteoprotegerin (OPG). The participants of visit 2, where 6315 subjects remained after exclusions, therefore constitute the study population in this paper.
We excluded persons with high values of hs-CRP, as we wanted to focus on low-grade inflammation.
AF cases diagnosed during the follow-up period (n=566) were identified as described earlier.

In the multivariable analysis, adjusted for traditional cardiovascular risk factors and other inflammatory biomarkers, we found that hs-CRP was associated with future AF in men (HR 1.14 for a 1 SD increase; 95% CI, 1.02–1.28), but not in women.

CRP is considered to reflect the burden of CVD, which is a known risk factor for AF. We therefore also performed analyses where we excluded patients with prevalent myocardial infarction (MI) at baseline. This did not change the results; neither did adjustment for ascertained MI during follow-up. Thus, the association between hs-CRP and future AF does not seem to be mediated by CVD in this study population.

We found a significant increase in AF across quartiles of WBCs in men (p=0.007) and in the total study population (p= 0.004). Subgroups of WBCs showed no significant associations with AF.

OPG is a novel biomarker which is associated with inflammation, vascular calcification, endothelial function, and atherosclerosis, and which has shown to be a marker of CVD.

OPG was associated with incident AF in a model adjusted for age and sex, and in an age-adjusted model for women. The significance was lost with further adjustment for CHD and other confounders. However, OPG was associated with AF in patients free of CHD at baseline, in multivariable analysis in the total study population.

Fibrinogen showed no significant association with AF.

Paper 3: Uric acid is associated with future atrial fibrillation

Uric acid (UA) has been shown to be associated with cardiovascular disease in population studies, but its relation to AF is largely unknown.

In Tromsø 4, UA was measured in visit 2. We were therefore able to study 6308 participants who were followed-up for eleven years. During this observation period, 572 persons were diagnosed with AF. When adjusted for cardiovascular risk factors and concomitant diseases, UA was associated with AF in both sexes, with higher estimates in women (though the difference between women and men did not reach statistical significance). Hazard ratio (HR) per 1 SD increase in SUA (91 μmol/L) was 1.40 (95 % confidence intervals [CI], 1.14-1.72) in women, and 1.17 (95 % CI, 1.02-1.36) in men. The upper quartile of SUA conferred a 76 % increased risk for AF in women and 49 % in men as compared to the lowest quartile.

SUA also exerts its effects through raised blood pressure, and inflammation, both of which are important risk factors for AF. We therefore adjusted for these risk factors in the analyses, as well as CVD and other risk factors for CVD. This did not change the estimates.

6. DISCUSSION OF METHODOLOGY

6.1 Study design

A cross-sectional study (survey) is a study of a defined population at a defined point of time. This is a useful design to study the prevalence of a disease, condition or risk factor. It is also useful for hypothesis generation, but not for hypothesis testing. Repeated cross-sectional studies can detect changes in risk factors and disease frequencies in populations over time.

The Tromsø Study is a prospective follow-up study of the general population in the municipality of Tromsø. It is also a longitudinal study, as the surveys have been repeated at regular intervals. Thus, the Tromsø Study combines the cross-sectional and the cohort study designs.

All risk factors or exposures are collected at baseline, when all individuals are "healthy", i.e. free of the condition we want to study. "Sick" or affected individuals are excluded from follow-up. The cohort is followed-up for a defined period of time, in this case eleven years, to see which individuals develop the condition or endpoint, in this case AF, and to assess possible risk factors for the condition.

6.2 Internal validity

This term refers to whether the results of a study are representative, true or valid for the population studied. Traditionally, two main problems need to be addressed here: bias and confounding.
Bias is a systematic deviation from the truth that distorts the results of research. This can occur in any process in any stage of a study, and produces a systematic error in the result.
Thus, bias can weaken a true association, or can produce a false association. Many forms of bias have been identified, but are often grouped into two main categories; selection bias and information bias. A total elimination of bias is not likely to achieve, as this would require a total degree of control. But through a thorough design and a careful conduct of study and analyses, bias can be reduced to a minimum, and the study can reach internal validity.

Selection bias will occur e.g. if the persons we want to study are not allocated in a standardized random way, and the groups we want to compare are actually different from the start. The association between exposure and outcome among those selected for analysis, for example the actual attendees of a population-based survey, may differ from the association among those who originally were invited. This kind of bias can be a problem in a population survey if the participation rate is low, and the individuals studied may not be representative of the entire population. Selection

bias can also occur if many participants are lost to follow-up. The design of the Tromsø Study, with the invitation of total birth cohorts and random samples, ensures a representative study population. High-risk individuals have been invited to sub-studies. The high attendance rates also help minimise selection bias, but we cannot exclude that the so-called healthy participant bias may have diluted the true associations between risk factors and outcome. The Regional Committee for Medical and Health Research Ethics does not permit analyses of non-attendees. However, we know from other studies that non-attendees may differ from those who attend a survey, in demographic characteristics and in prevalence of risk factors or diseases. (105, 106) In another Norwegian population-based study (the HUNT Study), the prevalence of common chronic diseases among non-participants was higher than in participants, and it is likely that the same is true for the Tromsø Study. (107)

Socio-economic status and education affect health awareness, life style and risk of disease. Non-attendees may be younger and healthier than the average participant (e.g. absent due to studies or lack of interest), or they may be older and sicker and therefore unable to attend. Non-attendees may also represent groups with lower health awareness and lower self-care abilities, and who tend to take less responsibility for own health.

Information bias and misclassification may occur during data collection, if the means for obtaining information about the subjects are inadequate. The main source of error is misclassification of exposure and/or outcome status. Misclassification of AF is an important possible source of bias in our study. Several steps were taken to ensure accurate classification of AF. Identification of possible cases was done through linkage to the University Hospital of North Norway (the only hospital in the area) and to the national Causes of Death Registry. In addition to the search for information on AF in the hospital records of all patients with a diagnostic code of AF or other relevant arrhythmia, we also performed systematic searches among patients with a diagnosis of CHD, stroke, or sudden or unexplained death. This led to the detection of many AF cases which would have been missed otherwise. Unfortunately, we did not register systematically the number of AF cases detected this way, but based on a similar search (related to the Tromsø-Iceland co-operative gene study) a rough estimate would be 100-120 cases, of the 822 cases in total, found in the study population in paper 1. However, we may still have missed a number of persons in our community with undiagnosed AF. Many AF patients are unaware of their arrhythmia and 5-40% of patients have been found to be asymptomatic. This is particularly common in older patients. (108) Many have the paroxysmal form which can be difficult to document on an ECG. Some AF patients may be taken care of by their family physician and have not been hospitalised with their AF.

It is difficult to give any assumption of the number of misclassifications due to non-detection. A British study from 1997 found that one third of AF patients were only seen by their general practitioner, and had not been hospitalised. (109) We have no such data from Norway. The referral pattern may differ, and may also have changed over time. Thus, the numbers cannot be inferred directly. It is also difficult to make assumptions about whether the AF group not seen in hospital is different from those who are referred. It could be speculated that those with symptomatic AF or with significant comorbidity would be referred, and that the non-referrals represent the healthier or asymptomatic group. On the other hand, younger people, i.e. those with presumed lone AF, might also be referred, as AF is an "abnormal" condition in the actual age group. The older people in whom the AF frequency is highest could be "spared" hospitalisation due to perceived lack of treatment consequences. It is also likely that the older patients, in whom AF symptoms more frequently are atypical or missing, will remain undiagnosed to a larger degree. This is likely to have caused an underestimation in our frequency analyses. If the old and asymptomatic, but co-morbid individuals are not detected, this could weaken the associations between the risk factors and AF.

All possible cases identified with a diagnosis of AF were validated by an endpoint committee, blinded for other information collected in the Tromsø Study. Only cases with information on documented AF in ECGs were classified as AF.

A possible misclassification problem should be mentioned regarding the biochemical analyses. Two of our predictor variables in the study of inflammation, hs-CRP and OPG, were analysed in frozen serum. The serum aliquots were stored for 12 years at -70°C and analysed without any freezing-thawing cycles before measurements. However, others have reported long-term stability of OPG when stored at -70°C. (110, 111) A study of CRP found that CRP values increased significantly, but slightly, after long-term frozen storage (112)

A *confounder* is a factor which is associated both with the exposure and the outcome variable, and which accounts for some or all of the observed relationship between the two. Confounding can thereby lead to under- or overestimation of an association. It may also change the direction of the effect, and it may obscure a true causal relationship. Examples of typical confounders are age and gender. As opposed to bias, confounding can be accounted for in statistical analyses. This can be done by stratification, e.g. by performing age- and sex specific analyses. Age adjusting is also a common method. Multiple regression analyses are frequently used to assess the effect of confounders. In our analyses, we have adjusted for known confounders such as traditional and more

novel cardiovascular risk factors. However, we obviously cannot fully exclude a confounding caused by unknown factors, for which we were unable to adjust.

6.3 External validity

This term refers to whether the results of a study are generalizable to other populations.

The design and the high attendance rates of the Tromsø Study have over years yielded results of high external validity and generalizability. The enrolment is based on the official population registry, thus ensuring that invitations are sent to the general population. The overall attendance rates have been high, 77-85% (with the exception of the sixth survey in 2007-08 when 66% of invited subjects attended). The vast majority of the participants have been of white, north-European ancestry, with few immigrants from other parts of the world, and the population of the Tromsø Study can therefore be assumed to be similar to other Caucasian populations, with similar prevalence of CVD and possibly also AF, and similar risk factors. There is only one hospital in this area, simplifying the identification of endpoints and ensuring that endpoints are reliable as far as possible. All inhabitants of Norway have a unique personal 11-digit identification number.

7. DISCUSSION OF MAIN RESULTS

7.1 Prevalence and incidence

Estimates of the total AF burden in our society are rough, and have been based on frequency analyses from other population studies (Framingham, Rotterdam, Copenhagen). These suggested a prevalence of approximately 1% in the total population. This may in reality be underestimated. A recent review presenting pooled analyses of population data suggest the prevalence more likely to be 2.5-3.5%. (24)

The frequency of AF has not been a main topic for the papers in this thesis. However, when the project was originally planned, we found it interesting to look into these numbers, as the prevalence of AF in a large, general Norwegian population had not been studied previously. I will therefore discuss briefly some of our findings.

Prevalence, total T4 population:
The cumulative prevalence of AF in the total cohort with a mean age of 46 years at baseline was 3.0 % in women and 4.2 % in men, for the total observation period.
The point prevalence at end of follow-up (December 31, 2007) was 2.2 % in women and 3.3 % in men (mean age 57 years).

Table 2. Point prevalence in age groups at end of follow-up

	Women			**Men**		
	Total cohort	**Atrial fibrillation**		Total cohort	**Atrial fibrillation**	
Age group	N	n	%	N	n	%
< 50	6272	17	0.3	5505	46	0.8
50-59	1569	43	2.7	1562	84	5.4
60-69	979	76	7.8	815	92	11.3
70-79	426	64	15.0	261	51	19.5
>80	37	2	5.4	7	0	0
total	9283	202	2.2	8150	273	3.3

This supports the overall pooled prevalence estimated by Ball and co-workers (24) in their review paper 2013 (men 0.033, women 0.024).

A direct comparison with the results found in other population studies is difficult, due to the age groups examined and the time of the study, as the prevalence has been reported to increase over time.

A cohort study of 75 year old inhabitants in two municipalities in southern Norway found a 10% prevalence of AF. (113) The table above shows a seemingly higher AF prevalence in our study population. However, this can partly be explained by the fact that the age groups here refer to the age at baseline, and the persons who developed AF were observed for a mean of 7.1 years before reaching their endpoint.

Incidence

The incidence rate for the total cohort (46 years at baseline) was 2.7 in women and 3.9 in men, per 1000 person-years. The incidence rate for the visit-2 population (60 years at baseline) was 7.2-7.3 in women and 9.5-9.6 in men. The populations in paper 2 and 3 are slightly different, due to exclusions. Hence, the incidence rates are also slightly different.

Our rates are apparently higher than what has previously been found in some other population studies. The Rotterdam Study, which analysed men aged 55-59 years, followed-up 1990 -99, found an incidence of 2.6. (33) There were no women in this age group of the study. In age group 60-64 years, the incidence was 4.9 for men and 2.1 for women.

In the Olmstead analyses from 2000, the age- and sex-adjusted incidence of AF per 1000 person-years was 3.7 (95% CI, 3.4 - 4.0). (23) This is a population with a high rate of North-European ancestry, which could therefore be presumed to be genetically similar to our population in Tromsø. Higher rates in the Tromsø Study could be attributed to a high level of detection. There is also a possibility that the incidence in our study population is higher, for genetic or other reasons, however, this remains speculative.

In the Reykjavik Study, for the observation period 1994-96, the incidence in age group 55-64 was 1.5 for women and 4.1 for men. (114)

In the Framingham Study, the incidence in the age group 55-64 years (which was the youngest) was 3.1 in men and 1.9 in women. (18, 37) Yet, these numbers date from an earlier study period (published 1994) and the incidence was found to increased in the proceeding years. However, it is likely that this increase partly can be explained by better detection methods. (34)

7.2 Traditional risk factors

In our study, we wanted to compare the risk factors for AF identified in other populations with the Tromsø Study participants (paper 1). Could we confirm the "traditional" risk factors? Would the associations be similar? Are there gender differences?

7.2.1 Age and gender

AF has been found to double in prevalence and incidence with each decade of age. (7) This is also confirmed in our study population. Ageing is accompanied by many changes in cardiac structure and function, as well as comorbidities known to predispose for AF. However, the increase in AF with age is seen also when adjusting for these conditions.
The reason for a male preponderance of AF risk is still unexplained. Most studies have found an approximately 1.5-fold higher risk among men, as was also confirmed in our analyses.

7.2.2 Hypertension

We could confirm that hypertension is a significant risk factor for AF. Raised blood pressure at baseline almost doubled the risk of AF in women and increased the risk by 40% in men. Other population studies have found a fairly similar risk in men and women. (7, 49) It is interesting to notice that a larger percentage of those who developed AF in our study, reported taking anti-hypertensive medication at baseline, but had in fact higher blood pressure than the non-treated. Therefore, hypertension that was not adequately treated could have contributed to the development of AF. In the 1980s and 1990s, the threshold for starting anti-hypertensive treatment was considerably higher than today, especially in older individuals, and target blood pressure was not much debated.
The increase in AF risk is relatively modest.The Framingham Heart Study reported an odds ratio of 1.5 in men and 1.4 in women. (37) The Manitoba Study found a relative risk of 2.3, (17) and the Malmö Diet and Cancer Study reported a hazard ratio of 1.8-1.7. (49) However, hypertension is the most prevalent independent and potentially modifiable risk factor for AF, (7) and up to 70% of patients with atrial fibrillation have a history of hypertension. (115) In our study, 80% of women and 70% of men who developed AF were hypertensive at baseline.

7.2.3 Coronary and other heart disease

Our study found that CHD is a strong risk factor, especially for men. This is in accordance with findings from the Framingham Study. (7) Moreover, valvular disease is a more frequent risk factor in

women, as also stated from Framingham. (37) We found that a higher percentage of women had valvular disease at the time of AF diagnosis (14.7% vs.12.8%). This difference was significant.

7.2.4 Other CHD risk factors

We found an inverse relation between total cholesterol and future AF. This has also been reported from the Cardiovascular Health Study in USA, (43) from Japan (116) and the ARIC study, USA. (117) The mechanisms for this are unknown. High blood lipids (total cholesterol and LDL cholesterol) are established risk factors for CHD, and statins are well documented in secondary prevention of CVD. Short term trials have indicated reduced odds for developing AF, however, there was significant heterogeneity between the trials. In longer and larger trials of statin versus control, no significant reduction in AF was found in a large meta-analysis published 2011. (118) Thus, trials have shown conflicting results or no effect on the prevention of AF. This could be in accordance with our and others' findings that cholesterol and future AF are inversely related. However, statins are shown to have other effects than lipid lowering, e.g. endothelium stabilizing and anti-inflammatory effects, which could act preventive.

7.2.5 Obesity

We could confirm that obesity (BMI) is a risk factor for AF. (Paper 1) This has been shown in many studies previously. (66, 67, 119) We found a clear gender difference in the impact of overweight, which was a stronger risk factor in men. This trend has been indicated in a few other studies. The Danish Diet, Cancer, and Health Study found a slightly higher risk in men than in women by increasing BMI. (67) A report from Framingham also found higher risk in men, but the significance was lost after adjustment for left atrial diameter. (66) Most studies of obesity as a risk factor for AF have not performed sex-specific analyses.
However, obesity has been reported to be a stronger risk factor in men, for incident AF related to acute myocardial infarction (120) and for AF after coronary artery bypass graft surgery. (121)
A recent report from Tromsø showed that men with overweight (BMI 25 kg/m² or more) were more prone to AF recurrence after ablation therapy (Espnes H. Atrial fibrillation ablation, Student assignment, UiT The Arctic University of Norway, Faculty of Health Sciences 2015).

Obesity can promote the development of AF through several ways. Obesity is associated with ischemic heart disease, higher blood pressure, insulin resistance and diabetes, increased inflammatory markers, and higher levels of uric acid. All of these have been found to increase the risk

for incident AF, also when adjusted for co-factors. It can be assumed that these obesity-related factors cause structural changes in atrial tissue.
A possible or probable link between obesity and AF could go via inflammation. Adipose tissue, which once was thought to be inert, has been proven to be highly metabolically active. Among other substances, adipocytes produce a number of inflammatory cytokines, which may contribute in generating a systemic inflammatory status. The topic of inflammation will be discussed later.

Visceral and pericardial fat has been much studied in recent years, and is known to imply a greater risk of metabolic and cardiovascular disorders than subcutaneous fat deposits. The Framingham Heart Study reported that pericardial fat volume predicts AF, independently of other measures of adiposity, including BMI. (122)
Obesity is linked to left atrial size, which is an independent predictor of AF onset. (66, 119, 123, 124) Obesity is also associated with thickening of the myocardium and ventricular diastolic dysfunction. (125, 126) Both of these are known risk factors for AF.
A large Danish study published 2013 showed that obesity is also a risk factor for AF in young fertile women. This group with a mean age of 30 years was essentially healthy and therefore had a low risk for incident AF. Still, the probability of AF was significantly greater for obese and very obese. (127)

An interesting study from Australia 2013 showed that weight loss decreased AF burden and severity. The control group received general lifestyle advice. During the 15 months of follow-up, a significant reduction in interventricular thickness and left atrial area was also documented in the weight reduction group. This is probably the first study to show beneficial effects on AF of risk factor management. (128)

7.2.6 Diabetes

We found that diabetes was a significant risk factor for AF in women. This is similar to a large American study which compared 17 000 diabetic patients with an equally large, age- and gender-matched group of non-diabetics in an observational cohort design. After controlling for other risk factors, diabetes was a highly significant risk factor for AF in women, but not in men. (70) A higher risk for AF in women was also shown from the Framingham study. (7) However, several studies have found a significant association between diabetes and AF, but have not performed sex-specific analyses. A meta-analysis of cohort and case-control studies, published 2011, found after adjustment for publication bias that patients with diabetes had a 34% greater risk of AF. Studies that had adjusted for multiple risk factors reported a smaller effect estimate compared to age-adjusted

studies. (129) The authors comment that the true risk between diabetes and subsequent AF therefore may be closer to 25%. A gender difference is not addressed.

Diabetes and AF share a number of common risk factors. These include obesity, hypertension, inflammation, obstructive sleep apnea and renal function deterioration. In addition, both conditions are associated with increased left atrial size, micro- and macrovascular changes, atherosclerosis and congestive heart failure. Diabetes and AF therefore are closely related.

The physiologic mechanisms linking diabetes and AF are not well elucidated. Diabetes is associated with left atrial enlargement and left ventricular hypertrophy, most prominent in women, (130) and with diastolic dysfunction. (131) Diabetes is associated with elevated CRP and other inflammatory markers, (76) which may promote myocardial fibrosis and diastolic dysfunction. Diabetes causes cardiac autonomic neuropathy, with remodelling and parasympathetic and sympathetic denervation, (132) thereby causing a direct effect on electrophysiological properties of atrial tissue.
Still, a dose-response effect has been demonstrated in a study by Dublin and co-workers 2010 in a population-based case-control study. (133) The AF risk was higher with longer duration of treated diabetes and worse glycaemic control. A dose-response effect is considered to support causality.
Insulin resistance (IR) has been much studied, as this is associated with incident CHD and also with inflammation and obesity. Some studies have indicated that IR could be an underlying mechanism in the development of AF in patients with type 2 diabetes. (134) However, a report from Framingham 2012 did not observe an association between IR and incident AF. (135)

Diabetes is increasing in society, and the influence on AF development is thereby likely to increase.

7.3 Palpitations

Our main novel finding in paper 1 was the importance of self-reported palpitations, which were frequent in the total cohort, especially in women. The prevalence of palpitations varies in different populations, dependent on definitions and diagnostic methods. However, palpitations are a frequent symptom in the general population, and have been found to be the cause of presenting to a GP in 16 % of visits. (136)

Palpitations reported at baseline increased the risk of AF in women by 62% and in men by 91%.
In our study, women reported more palpitations. This is similar to other studies. (72, 137) On the other hand, men who reported palpitations were more likely to be diagnosed with AF. It is interesting

to notice that the study from a GP setting in UK published in 2001 (137) also found that men presenting with palpitations were more likely (OR 2.1) to have a cardiac cause for their palpitations than did women.

What causes palpitations?

Aetiological causes are usually subdivided into five main groups: *cardiac arrhythmias, structural heart diseases, psychosomatic disorders, systemic diseases,* and *effects of drugs.* (71) Contractions of the heart which are too rapid, irregular or too slow will often (but not always) be registered as palpitations. Any type of tachyarrhythmia can give rise to palpitations, regardless of whether or not there is an underlying structural arrhythmogenic heart disease. Conditions associated with increased stroke volume, as in some structural heart diseases, and also in pregnancy, can cause palpitations. Also, the subjective perception of the heartbeat can be changed or anomalous in some individuals, thus causing an otherwise normal heart rhythm to be poorly tolerated, as in the case of some psychosomatic disorders.

Clinical studies have given conflicting information on the causes of palpitations, depending on the population studied. A much cited study from USA of 190 patients presenting in an emergency department or admitted to hospital because of palpitations, concluded that cardiac arrhythmias were diagnosed in 40%, psychosomatic in 30%, miscellaneous (systemic causes, structural heart disease, drugs) in 10%, and 16% remained unknown. (138) In a GP setting, only 19% had a clinically significant arrhythmia. (137) In a Norwegian study from a cardiac outpatient clinic, examining 198 consecutive patients with palpitations, a psychiatric/psychosomatic cause was diagnosed in 39%, CHD in 4%, while arrhythmias in need of treatment were not found. (139) Thus, palpitations can represent heterogeneous mechanisms, with highly different clinical implications.

Palpitations may indicate a predisposing substrate or early paroxysms of AF.

Premature atrial contractions (PACs) have been shown to precede AF (140, 141) and to be a surrogate marker for paroxysmal AF in patients with acute ischemic stroke. (142, 143) Excessive supraventricular ectopic activity in apparently healthy subjects was also associated with development of atrial fibrillation and with a poor prognosis in term of death or stroke, in a report from the Copenhagen Holter Study. (144)
A recent Swiss study found that PACs are common, as 99% of people over the age of 50 had at least one PAC on 24-hour Holter monitoring. The frequency of PACs is independently associated with age, history of cardiovascular disease, natriuretic peptide levels, physical activity and HDL cholesterol.

(145) Surprisingly, this study also found a significant association with body height and PACs. It has been hypothesised that tall individuals have larger atria, thereby increasing the risk for AF. This study could suggest that tall individuals also might have electrical alterations, making them prone to the development of AF. Of note, hypertension and BMI were not significantly related to PAC frequency. Although high blood pressure and obesity are two of the strongest risk factors for AF occurrence, this study might suggest that these two risk factors are exerting their effects via morphological means, but do not have much influence on the electrical part of AF.

Palpitations in our study:

The association between palpitations and AF raise two new questions.
Palpitations could be precursors of AF and basically caused by the same physiological and biochemical mechanisms, thereby also having common risk factors.
Or, palpitations are causally associated with atrial fibrillation (conditioning the atria), but caused by other factors than those associated with atrial fibrillation.

In order to investigate potential overlapping risk factors between palpitations and AF, we examined separately the predictors for palpitations and for AF (without including palpitations as a cofactor), in a cross-sectional logistic regression model. (Table 3.) We found that body height was a significant risk factor for both palpitations and AF. For palpitations, but not for AF, some significant risk factors were related to lifestyle (coffee, smoking). In contrast, the most prominent risk factors for atrial fibrillation were biological factors such as age, blood pressure, height, BMI, and for women also diabetes. Height, antihypertensive treatment and CHD were risk factors for both palpitations and atrial fibrillation. We therefore suggest that palpitations are probably causally associated with atrial fibrillation, but caused by other factors than those associated with atrial fibrillation.
The table also includes results when subjects with baseline CHD are excluded; this did not change the results.

Table 3. Risk factors for palpitations and AF, assessed separately

	OR sign. (p)							
Risk factor	**Palpitations**		**Palpitations**, baseline CHD excluded		**AF**		**AF**, baseline CHD excluded	
	Women	Men	Women	Men	Women	Men	Women	Men
Age (1 SD)	1.08 0.026	…	1.08 0.037	…	4.48 <0.0001	3.42 <0.0001	4.51 <0.0001	3.70 <0.0001
Systolic blood pressure (1 SD)	…	…	…	…	1.20 0.012	…	1.29 0.001	…
Heart rate (1 SD)	…	1.09 0.002	…	1.12 <0.0001	…	…	…	…
Height (1 SD)	1.14 0.001	1.12 0.003	1.15 <0.0001	1.13 0.004	1.30 0.040	1.37 <0.0001		1.19 <0.0001
Body mass index (1 SD)	…	…	…	…	1.27 <0.0001	1.59 <0.0001	1.24 0.003	1.52 <0.0001
Cholesterol (total) (1 SD)	…	1.09 0.011	…	1.08 0.021	…	…	…	…
HDL-cholesterol (1 SD)	…	…	…	0.92 0.027	…	1.21 0.004	…	1.10 0.001
Alcohol (1 SD)	…	1.08 <0.0001	…	1.09 <0.0001	…	…	…	…
Coffee (yes/no)	1.22 0.015	…	1.22 0.015	…	…	…	…	…
Smoking (yes/no)	1.19 0.001	1.36 <0.0001	1.20 <0.0001	1.34 <0.0001	…	0.76 0.037	…	0.72 0.030

Logistic regression model
Only significant results displayed

7.4 Inflammation

Inflammation has been shown in several studies to be associated with AF. (75-77) Whether inflammation is an initiator or a consequence or merely an association of AF is still debated. However, many studies support the concept that inflammation contributes to at least some types of AF. (76, 146)

When the Tromsø 4 survey was planned, around 1990, the attention towards inflammation as a risk factor for CVD was still only beginning to rise. Therefore, only a very limited selection of inflammatory biomarkers is available from this study: hs-CRP, OPG, WBC and fibrinogen. However, these biomarkers have been assessed in other studies, and we therefore wanted to make comparisons. (Paper 2.)

hs-CRP has proven to be a risk factor for cardiovascular disease in general, and also for AF in many studies. (76, 147) In our study, hs-CRP was associated with future AF in men. Other studies have reported hs-CRP to be an independent risk factor for future AF in both genders, although with varying strength of association. (75, 76) Most studies have not reported sex-specific analyses.

OPG has been increasingly studied as a marker of CVD. OPG is associated with inflammation, vascular calcification, endothelial function and atherosclerosis. OPG is also associated with diabetes, hypertension and obesity. (148) High plasma OPG is a strong predictor of CVD, ischemic stroke and total mortality, in high risk and general populations. (78) An association between OPG and AF could be linked via these conditions which are often co-existent with AF.
A study from the Framingham offspring cohort reported that a panel of 12 inflammatory markers predicted incident AF, but only OPG was significantly associated with AF. However, this relation lost its significance when myocardial infarction and heart failure were taken into account. (79) This appears to be in contrast with our study, as we found a significant association between OPG and AF in the total study population in the multivariable analysis, when excluding persons with pre-existing CHD or myocardial infarction. One could therefore speculate if a direct relation exists between OPG and AF in these CHD-healthy persons.

The level of **WBC** as a marker of future health outcomes in a general population has barely been investigated previously. We therefore wanted to study the impact of WBC on future AF. We found a significant increase in AF across quartiles of WBC in men, but not in women. Other publications on this topic seem to be lacking. However, several studies have reported the infiltration of WBC in the atria of AF patients, (74, 149) also in patients with lone AF without overt cardiovascular disease. The role of WBC in the development of AF remains undefined, but may promote structural and electrical remodelling by multiple mechanisms. These include the release of cytokines, and WBC are also an important source of reactive oxygen species (ROS) which stimulate fibroblasts.

Fibrinogen has been studied with conflicting results, but was found to predict future AF in the Copenhagen City Heart Study, (80) in the ARIC study (81) and the Women's Health Study. (77) A recent, large German study also reported that fibrinogen was significantly associated with AF in multivariable-adjusted models. (150) Others found no association between fibrinogen and future AF, (82, 83, 147) as was also the case in our study. The studies mentioned have been done in different age groups, and risk factor adjustment has also been performed differently. This could partly explain the apparently conflicting results.

The discussion of inflammation has been addressed thoroughly in paper 2.

7.5 Uric acid (UA)

An association between UA and future AF has been scarcely investigated until recent years. Whether UA is a cause of AF, or a confounder, is debated.

In paper 3, we found that baseline serum UA was associated with future AF, when adjusted for factors known to predispose for AF. The association was stronger in women than in men. Our results are partly in concordance with other studies. The first population-based prospective study to show an association between UA and future AF was published 2011 from the ARIC Study. (102) A recent meta-analysis by the same authors stated that high UA is associated with AF in both cross-sectional and cohort studies. (151) The relative risk of having AF for those with high UA was 1.67 (95% CI 1.23-2.27) compared with those with normal UA. A Japanese cross-sectional study published 2012 also found a relation between UA and AF in both genders, but the association after multivariable adjustments remained independent in women only. (103) The reason for this gender difference remains unexplained.

UA levels have also been shown to be associated with future AF in diabetic patients (152) and in patients with ischemic heart failure. (153)

UA is a marker of oxidative stress and a mediator of endothelial dysfuction, (154) and is associated with hypertension, CVD, obesity, inflammation, renal disease and diabetes. (155) All these conditions are known to represent risk factors for AF, and the association between UA and AF may therefore be linked through a number of ways. However, there is also evidence that UA is directly involved in the pathogenesis of these conditions. Elevated UA is a precursor of hypertension, and is known to activate the renin-angiotensin system. Clinical studies have shown that reducing UA with allopurinol (XO inhibitor) lowers blood pressure. (156) In CVD, treatment with allopurinol ameliorates angina. (157) Inflammation increases UA due to cell destruction. UA is therefore considered as a marker of inflammation. However, UA also activates pro-inflammatory cytokines and thereby promotes inflammation. (154, 158) Insulin reduces renal excretion of UA, however, hyperuricaemia often precedes the development of hyperinsulinaemia and diabetes, as well as obesity. (155)
A direct effect of UA on AF is also possible, and is supported by our study, as well as other studies mentioned above.

Population studies of UA have shown that mean levels in men increased gradually from the 1920s to the 1970s. (155) A recent analysis from USA (NHANES 2007-2008) showed that the prevalence of hyperuricaemia has increased substantially during the last decades. In this population with a mean

age of 47 years, 21% of both women and men had hyperuricaemia by definition. (98) In our study population with a mean age of 60 years, 15.3% of women had hyperuricaemia, and and 12.7% of men (> 350 µmol/L for women and > 450 µmol/L for men).
In the NHANES study mentioned above, hyperuricaemia showed stronger associations with comorbidities among women than among men. It is suggested that the relative physiologic impact of hyperuricaemia may be stronger in women.
Thus, the prevalence of hyperuricaemia has increased substantially during the last decades.The associated comorbidities increase accordingly, with a corresponding impact on society's health cost.

7.6 Lone atrial fibrillation (Lone AF)

We wanted to focus on lone AF, which has been investigated incompletely previously (paper 1). This term was first introduced in 1953, referring to AF subjects in whom heart disease could not be demonstrated. During the last decades, as defined in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, the term "lone AF" generally applies to young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. (159) Hence, lone AF is a diagnosis of exclusion.

As expected, a low percentage in our study was found to have lone AF, as this applied to only 4.4% of the female and 7.2% of the male AF patients. In previous studies, the prevalence of lone AF has been estimated to 2-30 %. (160, 161) This is presumably due to large heterogeneity of the populations studied, and possibly insufficient information about concomitant disease.
In our study population, 67% of lone AF patients were male. This is in concordance with other studies, which have found the male preponderance to be 70-80 %. (160)

Individuals with lone AF have been reported to be taller and leaner than other AF patients. In our study, men with lone AF were tall, but not lean. We also found a significant relation between BMI and lone AF in men. To our knowledge, this has not been shown earlier.
We also found that height was a risk factor for lone AF in men. Women with lone AF seemed to be taller and leaner (than AF women in general), but probably due to a low number in this group (n=16), these differences were not significant.

Premature atrial contractions (PACs) have been shown to increase the risk of AF and stroke.

A study from Switzerland 2012 found that PACs were associated with body height. (145) Tall individuals are presumed to have larger atria, thereby increasing the risk for AF. This Swiss study could suggest that tall individuals also might have electrical alterations, thereby increasing the risk for development of AF. One may speculate that this could play a role in cases of lone AF.

High-impact physical activity has been found to be associated with AF, especially lone AF type. In our study population, too few participants reported such level of activity, and we are not able to draw any conclusions in this field.

Our subgroup of lone AF is small, and conclusions are therefore uncertain. Moreover, in our analyses of lone AF, we lacked information about some risk factors for AF, such as pulmonary disease, obstructive sleep apnea, peripheral artery disease, chronic kidney disease, and inflammation. The exclusion of cardiac diseases in this group is based on data from their medical records, but echocardiography had not been performed. It is therefore possible that our group is not completely “pure”, but may contain persons with concomitant or subclinical disease.

As already mentioned, lone AF has previously been considered to occur in healthy individuals without identifiable risk factors. Whether lone AF really exixts, or depends on how hard one looks for concomitant conditions, has been much debated. Growing insight into the diversity of numerous mechanisms involved in the pathogenesis of AF suggests that apparently lone AF might not be so "lone" in many patients. Atrial stretch, inflammation and oxidative stress have all been demonstrated in young individuals with presumed lone AF. (162) A genetic predisposition is likely and appears to play a stronger part in lone AF than in AF in general. Population studies have shown familial clustering of AF in young and heart-healthy individuals. Studies have also demonstrated several gene variants which are asociated with lone AF. (163, 164)

The increasing evidence that even “lone” AF is associated with changes in cardiac structure and function, makes the lone AF term less meaningful. However, these patients have shown to have a lower risk for thromboembolism and mortality, and therfore do not require the same anticoagulant treatment as older patients with comorbid conditions. Yet, they need regular follow-up to assess any new risk factors presenting.

7.7 Gender differences

The words “sex” and “gender” are commonly used interchangeably in epidemiology. Other medical, psychological and social research fields distinguish between “sex” as the biological characteristic and “gender” as a social and cultural concept.

For many years, women were underrepresented in many medical studies. Therefore, they provided very few endpoints, e.g. in the cardiovascular field. As a result of this, the knowledge of diseases and their frequencies and clinical courses in women has been poorly acknowledged or understood. This is also the case for treatment strategies and the effects of pharmacologic intervention.
The last couple of decades have provided increasing evidence that male and female hearts are different in many aspects. The differences may be subtle, sometimes without clinical consequences, but in other connections of significance. As an example of this, many cardiovascular drugs have been found to have somewhat different therapeutic and adverse effects in men and women. (165) Women have a higher resting heart rate and a shorter sinus node recovery time. Women have longer QT interval and are more susceptible to ‘torsade de pointes’- arrhythmia when administered certain anti-arrhythmic drugs.

However, a reason why women should be less prone to AF, remains unknown.

Many studies have found that risk factors for AF are differently distributed in women and men, and that the risk factors show various strength of association in the two genders. However, these differences have not been fully consistent through the studies. This could be explained by differences in the populations studied, and that adjustment for confounders has been done differently. The adjustment for gender as a confounder is important, but often not sufficient.

Women with AF have demonstrated a poorer outcome than do men. Women have higher cardiovascular and all-cause mortality, as demonstrated in the large population studies of Framingham and Renfrew/Paisley. (166, 167) Studies have also shown that women have higher risk of AF-related stroke, (36, 167) and strokes are more severe in women, with poorer outcome. Women with AF report symptoms, palpitations included, to a larger extent than do men, and experience a lower quality of life. (35, 168, 169)

In our analyses, we found different strengths of association in women and men for many of the variables analysed. This has been discussed previously in this thesis, in the passages concerning the different risk facors, and will only be briefly mentioned here:

Hypertension, diabetes and uric acid are stronger risk factors for AF in women.

CHD and overweight are stronger risk factors for men. Inflammation may be of greater importance in men, as we found the biomarkers hs-CRP and WBC to be associated with future AF in men only.

Palpitations, although more frequent in women, was a stronger risk factor for AF in men in our study.

8. CONCLUSIONS

In this large, general Norwegian population from the Tromsø Study, we have shown that AF is more frequent than what has been assumed formerly, as 2.2% of women and 3.3% of men in our study were diagnosed with AF.

A main new finding was the importance of self-reported palpitations as a risk factor for AF, which has not been shown earlier. We confirmed that hypertension, overweight, diabetes and CHD were important risk factors. This is in accordane with other studies.

Among the four available inflammatory biomarkers, we found a significant increase in AF across quartiles of WBC. This has not been shown earlier. hs-CRP was associated with AF in men. OPG was associated with AF in persons without CHD. Fibrinogen showed no association with AF in our study population.

Uric acid was a strong risk factor for AF.

Our study has confirmed the need for sex-specific analyses in medical research. We found different strength of associations in women and men for several variables.

Palpitations showed a stronger association with AF in men, although this symptom is more frequent in women.

Hypertension, diabetes and uric acid were stronger risk factors for AF in women.

CHD and overweight were stronger risk factors in men. Inflammation may be of greater importance in men.

Low physical activity, vigorous exercise, smoking and use of alcohol showed no association with AF in this population.

9. IMPLICATIONS

AF is a common arrhythmia, conferring considerable morbidity with the consequent need for medical care. AF occurrence has increased during the last decades, and is expected to rise further, with a rising proportion of the older population, and improved and prolonged survival from previously fatal cardiovascular conditions.

The investigation of risk factors is important, with the purpose to identify those that are potentially modifiable.

Still, the question remains whether correcting risk factors reduce AF risk. From clinical studies we now have evidence that weight loss reduces AF burden and severity. (128) Treatment of hypertension has proved favourable in other areas, e.g. in prevention of heart failure and stroke. A favourable effect in prevention of AF can therefore be expected. The prevention and treatment of cardiac disease in general is equally important, as is the prevention of diabetes and overweight.

The importance of inflammatory states is still not conclusive, and needs further research.

The association of uric acid and future AF is interesting and intriguing, and raises the question whether treatment with uric acid lowering agents could reduce the risk for AF. This should be investigated in clinical studies.

Updated endpoints (1994-2012) for our study population are now available. Re-analyses of data are therefore possible and interesting, to address any stronger or other associations.

Other variables are also available and now under research.

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Appendix 1

Figure:
The Tromsø Study, cohort profile

Cohort profile: The Tromsø Study

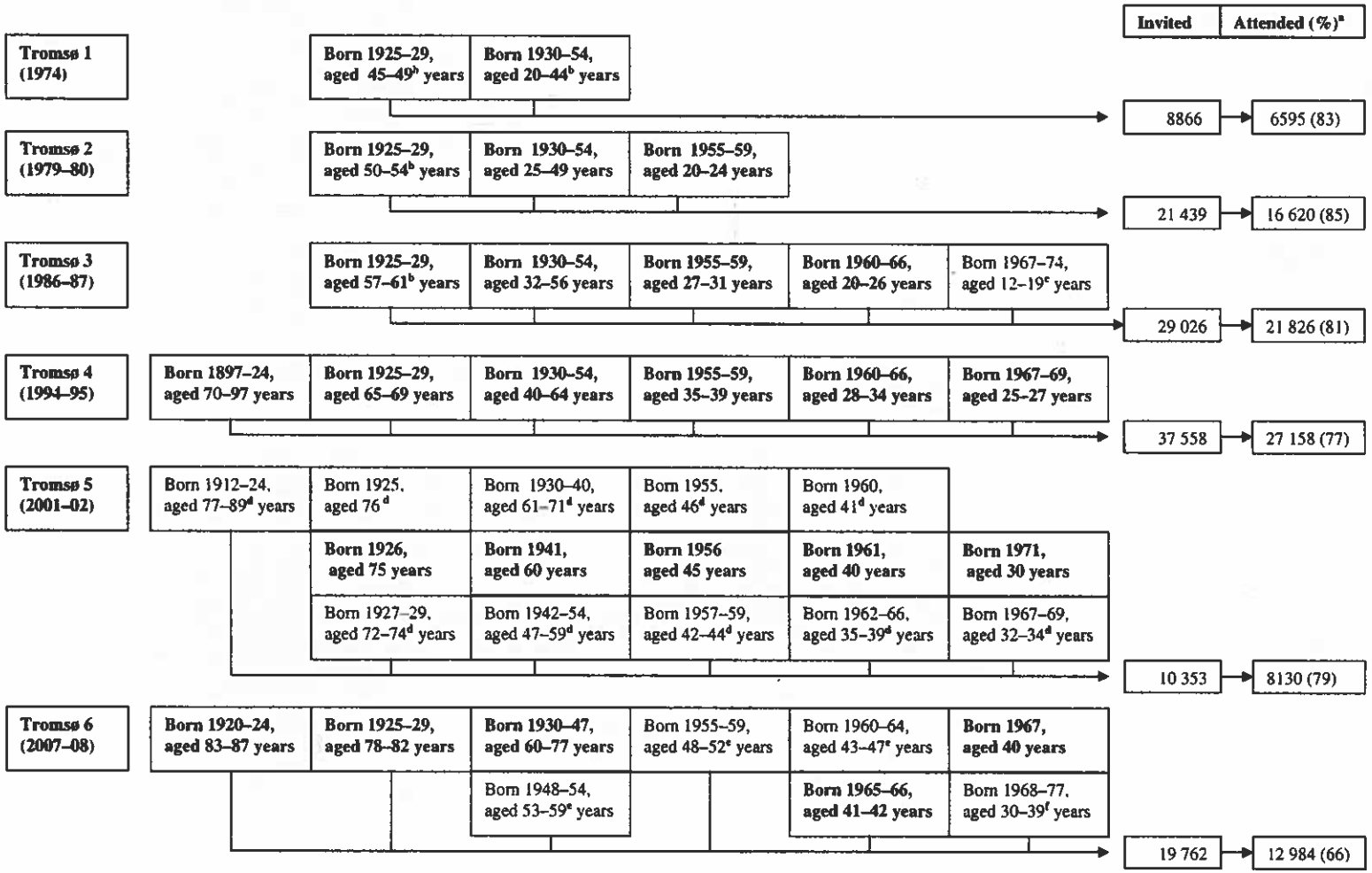


Figure 1 The Tromsø Study. Invitation by birth cohort and attained age in Tromsø 1–6. Invitation of total birth cohorts is marked as **bold**, shading indicates that samples of birth cohorts were invited. [a]Adjusted for deaths, emigration from Tromsø during the survey period etc. [b]Men only. [c]10% of total birth cohort and offspring of high-risk men who participated in a family intervention trial after the second survey. [d]Restricted to those who participated in the second visit in Tromsø 4. [e] 40% of the total birth cohorts. [f]10% of the total birth cohorts

Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromsø Study. Int J Epidemiol. 2012;41(4):961-7.

Appendix 2

Table:

Brief overview of data collected in the different surveys that form the Tromsø Study

Cohort profile: The Tromsø Study

Brief overview of data collected in the different surveys that form the Tromsø Study

	Tromsø Study survey number					
Type of information[a]	1	2	3	4	5	6
Marital status, age, sex	x	x	x	x	x	x
Questionnaire data	x	x	x	x	x	x
Interview	x	x	x	x	x	x
Measured weight and height	x	x	x	x	x	x
Measured waist and hip circumference				x	x	x
Measured blood pressure	x	x	x	x	x	x
Blood sample (blood lipids)	x	x	x	x	x	x
Blood sample (hormones)				x	x	x
Blood samples (haematology)				x	x	x
Blood samples (other blood analyses)			x	x	x	x
Electrocardiography (ECG)			x	x	x	x
Echocardiography				x	x	x
Ultrasound examination of the carotid artery				x	x	x
Ultrasound examination of the abdominal aorta				x	x	
Spirometry					x	x
Bone mineral densitometry				x	x	x
Urinary analyses (microalbuminuria)				x	x	x
Examination of sight (visual acuity)					x	x
Examination of number of falls					x	
Cognitive testing					x	x
Retinal photography, optical coherence tomography						x
Pain sensitivity						x

[a]Note that some of the examinations have been conducted only in parts of the population. For a close to complete overview of the data collected, please see our website (http://tromsoundersokelsen.uit.no/tromso/).

Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromsø Study. Int J Epidemiol. 2012;41(4):961-7.

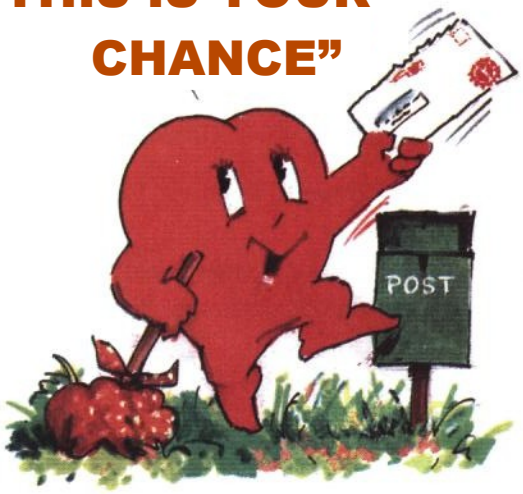
Appendix 3a

Questionnaire Tromsø 4

Visit 1, all

HEALTH SURVEY
Invitation

"THIS IS YOUR CHANCE"



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

Welcome to the Tromsø Health Survey!

The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

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

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

Yours sincerely,
Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service

"THIS IS A REAL OPPORTUNITY- TAKE IT!"

YOUR OWN HEALTH

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

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

Do you have, or have you had:

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

Do you use blood pressure lowering drugs?

Currently	28	1
Previously, but not now		2
Never used		3

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months? 29 Yes / No

Have you in the last two weeks felt:

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

SMOKING

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

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

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

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

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

Do you yourself smoke:

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

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

If you currently smoke, or have smoked previously:

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

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

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

EXERCISE

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year.*

Time spent going to work counts as leisure time.

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

COFFEE

How many cups of coffee do you drink daily?

Put 0 if you do not drink coffee daily.

Coarsely ground coffee for brewing 58 ____ Cups

Other coffee 60 ____ Cups

ALCOHOL

Are you a teetotaller? 62 Yes / No

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

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

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

Do not count low-alcohol beer.

Put 0 if less than once a month.

Beer	Wine	Spirits
Glasses	Glasses	Glasses

FAT

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

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

EDUCATION/WORK

What is the highest level of education you have completed?

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

What is your current work situation?

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

How many hours of paid work do you have per week? 77 ____ No. of hours

Do you receive any of the following benefits?

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

ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)? 85

Yes	No	Don't know

Appendix 3b

Questionnaire Tromsø 4

Visit 2, persons < 70 years

The Tromsø Health Survey

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

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

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

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

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health Screening Service

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

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

Day Month Year

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

CHILDHOOD/YOUTH

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

..... 24 - 28

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

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

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

How many of the first three years of your life

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

How many of the first 15 years of your life

- did you live in a town/city? ..... 32 ____years
- did your family have a cat or dog in the home? ..... 34 ____years

HOME

Who do you live with?

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

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

What type of house do you live in?

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

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

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

		Yes	No
Has your house been insulated after 1970?	53	☐	☐
Do you live on the lower ground floor/basement?	54	☐	☐
If "Yes", is the floor laid on concrete?	55	☐	☐

What is the main source of heat in your home?

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

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

WORK

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

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

Can you decide yourself how your work should be organised?

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

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

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

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

YOUR OWN ILLNESSES

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

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

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

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

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

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

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

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

SYMPTOMS

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

How often do you suffer from sleeplessness?

Never, or just a few times a year 186	❑ 1
1-2 times a month	❑ 2
Approximately once a week	❑ 3
More than once a week	❑ 4

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

No particular time of year 187	❑ 1
Especially during the polar night	❑ 2
Especially during the midnight sun season	❑ 3
Especially in spring and autumn	❑ 4

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

How often do you suffer from headaches?

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

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

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

USE OF HEALTH SERVICES

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

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

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
*Put **0** for items you have **not** used.*

Medicines

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

Dietary supplements

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

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

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

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 _____ good friends
Do not count people you live with, but do include other relatives!

How many of these good friends do you have contact with at least once a month? ..... 261 _____

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

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

Never, or just a few times a year	264	❑ 1
1-2 times a month		❑ 2
Approximately once a week		❑ 3
More than once a week		❑ 4

FOOD HABITS

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

A catering portion is enough for about ..... 265 _____ slices

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

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

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

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

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs?
*Tick one box for **each** foodstuff.*

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

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

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

ALCOHOL

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

Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not at all the last year ..... ❑ 1
- A few times ..... ❑ 2
- 1-2 times a month ..... ❑ 3
- 1-2 times a week ..... ❑ 4
- 3 or more times a week ..... ❑ 5

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

WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? Write **0** if you never have.

- before age 20 ..... 314 _____ times
- later ..... 316 _____ times

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

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

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

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

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

Your comments:

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 326 _____years

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

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? ..... 330 Yes ❑ No ❑

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

If you still menstruate or are pregnant:

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

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

PREGNANCY

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

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

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

If "Yes", during which pregnancy?

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

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

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

CONTRACEPTION AND ESTROGEN

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

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

376 .....

If you use or have ever used oral contraceptive pills:

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

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

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

If you have stopped taking the pill:

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

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

The Tromsø Health Survey

Appendix 3c

Questionnaire Tromsø 4

Visit 3, persons > 70 years

Tromsø Health Survey
for the over 70s

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

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

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

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

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

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

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

Day Month Year

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

CHILDHOOD/YOUTH

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

.....24 -28

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

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

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

How old were your parents when they died?

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

HOME

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

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

What type of house do you live in?

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

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

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

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

PREVIOUS WORK AND FINANCIAL SITUATION

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

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

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

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

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

What kind of pension do you have?

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

How is your current financial situation?

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

HEALTH AND ILLNESS

Has your state of health changed in the last year?

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

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

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

YOUR OWN ILLNESSES

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

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

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

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

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

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

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

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

SYMPTOMS

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

How often do you suffer from sleeplessness?

- Never, or just a few times a year .....196 ❑ 1
- 1-2 times a month ..... ❑ 2
- Approximately once a week ..... ❑ 3
- More than once a week ..... ❑ 4

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

- No particular time of year .....197 ❑ 1
- Especially during the polar night ..... ❑ 2
- Especially during the midnight sun season ..... ❑ 3
- Especially in spring and autumn ..... ❑ 4

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

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

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

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

BODILY FUNCTIONS

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

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

Are you dependent on any of the following aids? ?

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

USE OF HEALTH SERVICES

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

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

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

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

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

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

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

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

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the last year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
Put 0 for items you have not used.

Medicines:

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

Dietary supplements:

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

FAMILY AND FRIENDS

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

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

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

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

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

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

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

- Never, or just a few times a year ..... 301 ☐ 1
- 1-2 times a month ..... ☐ 2
- Approximately once a week ..... ☐ 3
- More than once a week ..... ☐ 4

FOOD HABITS

Number

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

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

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

Tick one or two boxes.

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

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

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

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

Tick one box for each foodstuff.

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

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

Tick for all foodstuffs listed.

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

WELL BEING

How content do you generally feel with growing old?

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

What is your view of the future?

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

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

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

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

PREGNANCY

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

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

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

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

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

ESTROGEN

Do you use, or have you ever used estrogen:

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

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

..... 373

Your comments:

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

Tromsø Health Survey