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THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences, Department of Community Medicine

Atrial Fibrillation: A prospective population study of risk factors and complications

The Tromsø Study

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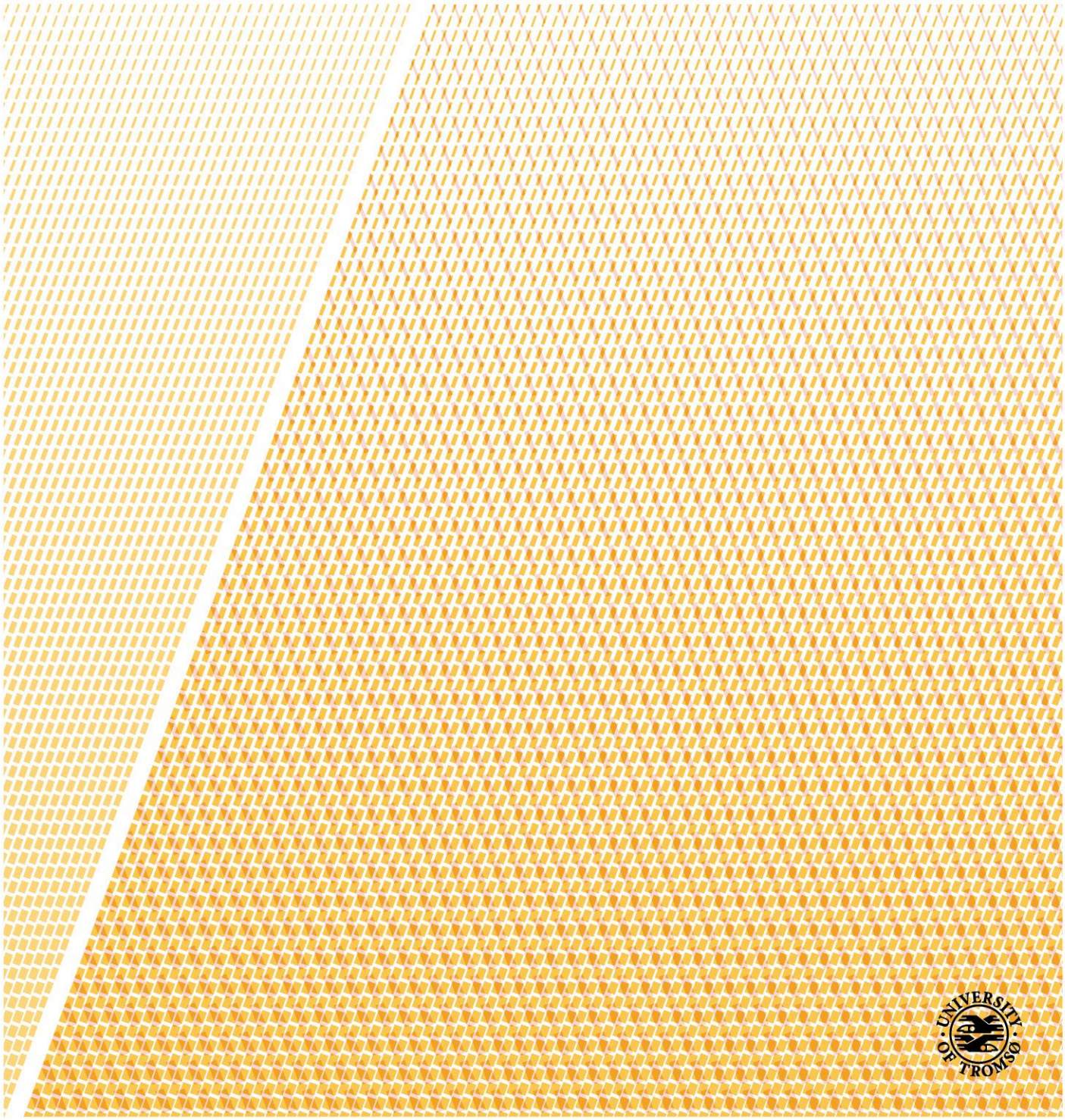
Sweta Tiwari

A dissertation for the degree of Philosophiae Doctor – January 2018



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Tromsø, January 2018

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Summary

Background: Atrial Fibrillation (AF) is the most common arrhythmia associated with increased mortality and morbidity. It increases the lifetime risk of stroke and heart failure and affects one's quality of life and cognition. There is a need for studies on risk factors and consequences for AF in large general population cohorts with long follow-up from various populations.

Objective: To investigate diastolic dysfunction as risk factor for AF and AF as a risk factor for stroke and cognitive decline in a prospective population study.

Methods: Participants from the population-based Tromsø Study were used as study sample. From the fourth survey (1994-95), 2406 participants who were free from AF at baseline, were followed until 2010 to examine the association between diastolic dysfunction, measured by echocardiography at baseline, and AF. From the same survey, 2844 participants free from stroke at baseline, were followed until 2012 to examine the association between AF and stroke, independently of other risk factors. From the fifth (2001) and sixth (2007-08) survey, 2491 participants with repeated cognitive screening were followed prospectively to examine AF as a risk factor for cognitive decline.

Main results: Enlarged left atria (LA) as a measure of diastolic dysfunction gave a fourfold increased risk of AF in both sexes, and adding measures of abnormal diastolic flow increased the predictive ability significantly. When enlarged LA size was combined with CHA_2DS_2-VASc score ≥ 1, participants had nine times increased odds of stroke regardless of AF status. In stroke free participants, AF was significantly associated with 40% larger cognitive decline as measured with the tapping test.

Conclusions: Diastolic dysfunction was found to be a risk factor for AF mainly through enlarged LA. Enlarged LA and CHA_2DS_2-VASc score $\geq$1was a strong predictor for stroke, regardless of AF status. Repeated cognitive screening measured with the tapping test found AF as a risk factor for cognitive decline. Our findings suggest closer clinical monitoring of patients with CHA_2DS_2-VASc score $\geq$1 and Holter monitoring in people with no known AF but with increased risk of stroke and cognitive decline.

Sammendrag

Bakgrunn: Atrieflimmer er den vanligste hjertearytmi i befolkningen, og er forbundet med økt sykelighet og dødelighet. Atrieflimmer øker risiko for hjerneslag og hjertesvikt, og påvirker livskvalitet og kognitiv funksjon. Det er behov for flere studier av risikofaktorer og konsekvenser for atrieflimmer i store befolkningskohorter med lang oppfølgingstid.

Hensikt: Å undersøke diastolisk dysfunksjon som risikofaktorer for atrieflimmer, og atrieflimmer som en risikofaktor for hjerneslag og kognitiv svikt i en prospektiv befolkningsundersøkelse.

Metoder: Deltakere i studien er fra den befolkningsbaserte Tromsøundersøkelsen. Fra den fjerde Tromsøundersøkelsen (1994-95) ble 2406 menn og kvinner, som ikke hadde atrieflimmer ved studiestart, fulgt ut 2010 for å undersøke sammenhengen mellom atrieflimmer og diastolisk dysfunksjon, målt ved ekkokardiografi i 1994. Fra samme undersøkelse ble 2844 deltakere, uten hjerneslag, fulgt ut 2012 for å undersøke sammenhengen mellom atrieflimmer og hjerneslag. Fra den femte (2001) og sjette (2007-08) Tromsøundersøkelsen ble 2491 deltakere med data fra repeterte kognitive tester fulgt prospektivt for å undersøke om AF var en risikofaktor for svekket kognitiv funksjon.

Resultater: Forstørret venstre atrium som et mål for diastolisk dysfunksjon hadde en fire ganger økt risiko for utvikling av atrieflimmer hos begge kjønn. Når forstørret venstre atrium ble kombinert med CHA_2DS_2-VASc-score ≥ 1 hadde deltakerne ni ganger økt odds for å få hjerneslag, uavhengig av om de hadde atrieflimmer. Hos deltakere uten hjerneslag medførte AF 40% større kognitiv reduksjon målt ved tappetesting.

Konklusjoner: Diastolisk dysfunksjon målt ved forstørret venstre atrium, ble funnet å være en risikofaktor for atrieflimmer. Forstørret venstre atrium og CHA_2DS_2-VASc-score ≥1 var en sterk prediktor for hjerneslag, uavhengig av atrieflimmerstatus. Atrieflimmer var en risikofaktor for redusert kognitiv funksjon målt med tappetest. Våre funn gir grunnlag for å anbefale klinisk monitorering av pasienter med CHA_2DS_2-VASc score ≥1 og Holter-monitorering av personer uten kjent atrieflimmer, men med økt risiko for hjerneslag og kognitiv svikt.

Abbreviations

AF - atrial fibrillation

AFL – atrial flutter

BMI - body mass index

E/A ratio - ratio of peak early left ventricular (LV) filling (E-wave) and peak late LV filling (A-wave)

ECG - electrocardiogram

EDT - E-wave deceleration time

HDL - high-density lipoprotein

HR - hazard ratio

LA - left atrium

LV - left ventricle

LVH - left ventricular hypertrophy

MCI - mild cognitive impairment

MI - myocardial infarction

SA - sinoatrial

List of papers

Paper I

Tiwari S, Schirmer H, Jacobsen BK, Hopstock LA, Nyrnes A, Heggelund G, Njølstad I, Mathiesen EB, Løchen ML. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010. Heart. 2015;101:1302-1308

Paper II

Tiwari S, Løchen ML, Jacobsen BK, Hopstock LA, Nyrnes A, Njølstad I, Mathiesen EB, Schirmer H. CHA_2DS_2-VASc score, left atrial size and atrial fibrillation as stroke risk factors in the Tromsø Study. Open Heart. 2016;3(2):e000439

Paper III

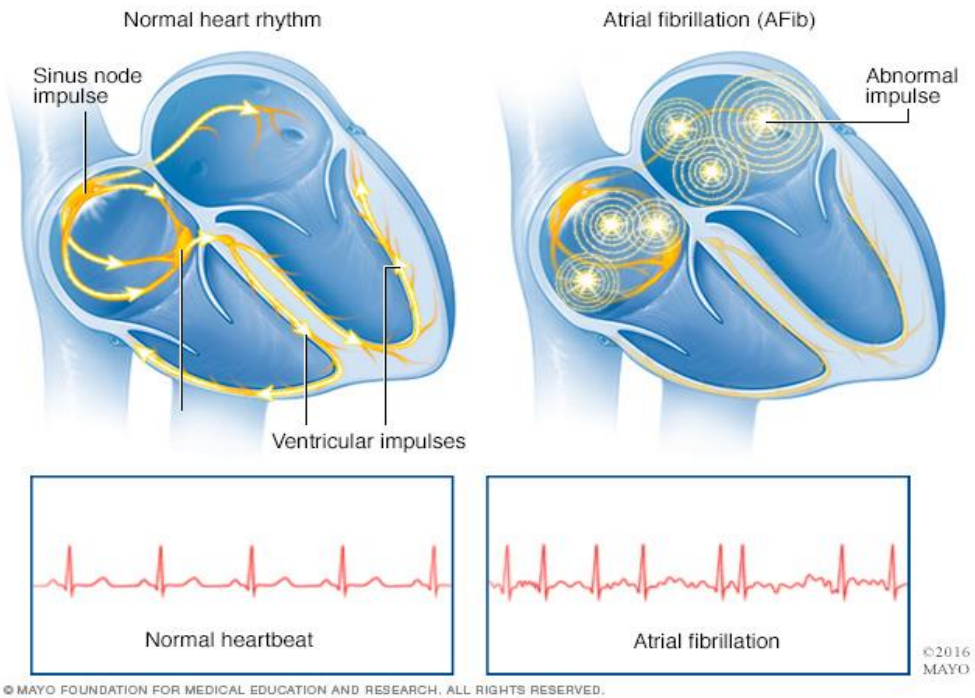
Tiwari S, Løchen ML, Jacobsen BK, Hopstock LA, Nyrnes A, Njølstad I, Mathiesen EB, Arntzen KA, Ball J, Stewart S, Wilsgaard T, Schirmer H. Atrial fibrillation is associated with cognitive decline in stroke-free subjects: The Tromsø Study. European Journal of Neurology. 2017;24:1485-1492

1. Introduction

1.1 Atrial fibrillation

Atrial fibrillation (AF) is the most common abnormal heart rhythm in which the atria quiver in an irregular pattern and the blood flow slows down or stagnates leading to blood clots, stroke, heart failure and other complications (1). AF often influences quality of life as it may be associated with disability, cognitive impairment, anxiety, dyspnea, chest pain, hospitalization and absence from work (2). In each heartbeat, an electric signal spreads from the top of the heart to the bottom, which causes the heart to contract and pump blood. Each electrical signal begins in a group of cells called the sinus node or sinoatrial (SA) node. In AF, the signal does not begin in the SA node but in other parts of the atria or in the nearby pulmonary veins. The signals do not travel normally and may spread throughout the atria in a rapid and disorganized way, causing AF as shown in Figure 1 (3).

Figure 1. Normal heartbeat and atrial fibrillation (4).



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In terms of presentation, duration and spontaneous termination, AF is classified into groups as following: (5)

- First diagnosed AF: AF not diagnosed before, irrespective of duration, presence or severity of symptoms.
- Paroxysmal AF: self-terminating AF, i.e. spontaneous restoration to normal within 48 hours or less than seven days.
- Persistent AF: AF that last longer than one week, not self-terminating, needs medical or electrical cardioversion after seven days or more.
- Long-standing persistent AF: persistent AF lasting for one year or more.
- Permanent AF: persistent and long-standing AF in which restoration to normal rhythm is no longer possible.

1.2 Epidemiology of atrial fibrillation

AF is a common public health problem, the prevalence of which is expected to increase threefold in the next three decades (6). In general adult populations of Europe, the prevalence ranges from 0.12-0.16% in subjects younger than 50 years, 3.7-4.2% among subjects aged 60-70 years and 10-17% among those 80 years or older (2). Similar numbers are found in Norwegian cohorts (7-9). The estimated prevalence does not include those with silent AF, which means there might be many more cases than the estimated number. The estimated number of new AF cases per

year worldwide is 2 million for women and 2.7 million for men (10). In the Tromsø Study (1995-2007), in subjects with mean age of 46 years at baseline the incidence rate was 2.7 in women and 3.9 in men, per 1000 person-years (9). In contrast to other studies (10-12), an unpublished study performed in the Tromsø population from 1986-2011 does not show increase in age-adjusted AF incidence from 2006-2011 (13). This finding is supported by a study performed in another Northern European population from 1991-2008 in which the increase in AF incidence was found only among women but not in men (14). Both prevalence and incidence rates are twofold higher in developed regions compared with developing countries, and are higher in men than women (10).

The rising unadjusted prevalence and incidence of AF can be partly explained by demographic transition to an inverted age pyramid as frequency of AF increases with advancing age (10). However, even after adjusting for age, gender and other comorbidities, several studies have found increasing incidence and prevalence of AF, suggesting additional factors influencing the frequency of the disease (12, 15). The risk of AF increases in men (especially with lower socio-economic status), smokers, those with increased alcohol intake or obesity (16-18). In addition, the increase in AF incidence and prevalence may also be due to greater awareness, improved ability to diagnose AF through enhanced surveillance and increased ability to treat chronic diseases (2, 11). With decline in risk factors for AF and increased longevity due to increased ability to treat disease, this might overestimate the AF burden in the years to come.

1.2.1 Diastolic dysfunction and relation to atrial fibrillation

Diastole is the relaxation phase of the cardiac cycle when the heart muscle fills with blood. Left ventricular (LV) diastolic dysfunction occurs as a result of impaired LV relaxation and increased LV chamber stiffness which increases cardiac filling pressures (19). Assessment of diastolic dysfunction is ideally performed by Doppler echocardiography mainly because it is widely available, non-invasive and less expensive compared to other techniques (20). The assessment of diastolic dysfunction includes investigating mitral and pulmonary flow velocities, evaluation of mitral annular motion by tissue Doppler imaging and left atrial (LA) size estimation (21-23).

The early (E) and late (A) diastolic filling velocities, the E/A ratio, and the E deceleration time (DT) are the mitral inflow indices that assess diastolic dysfunction through echocardiography. The E/A ratio and EDT are used to identify the filling patterns. The E-wave refers to the pressure gradient between LA and LV during early diastole, which is affected by alterations in the rate of LV relaxation and LA pressure (19). The A-wave refers to the pressure gradient between LA and LV during late diastole, which is affected by LV compliance and LA contractile function (19). The EDT is the duration of the interval between peak early diastolic filling and the end of E-wave. EDT is influenced by LV relaxation, LV diastolic pressures and LV stiffness (19). LA size reflects the mean pulmonary wedge pressure and hence is a sensitive marker of chronic diastolic dysfunction (20). The filling patterns are categorized as impaired relaxation, normal or pseudonormal filling and restrictive filling.

Several studies have shown higher risk of AF among those with larger LA (24-27). LA size does not change with ageing, thus enlargement is an expression of pathology (28). LA enlargement is due to the change in filling dynamics associated with

abnormal LV relaxation, which decreases passive emptying volume from the LA to the LV and decreased direct flow volume from pulmonary veins into the LV in early diastole. To compensate, active LA contraction is enhanced, increasing the active emptying volume in late diastole. This preserves the LV stroke volume, but it also enlarges the LA predisposing to AF (29). Other studies have also found an association between diastolic dysfunction and risk of AF (25, 30). The major risk factors for LA enlargement in the general population are hypertension, obesity and diabetes, which are also risk factors for AF (31, 32).

1.3 Clinical implications of atrial fibrillation

The diagnosis of AF needs confirmation by an electrocardiogram (ECG). ECG characteristics include irregular R-R intervals and absence of distinct repeating P waves. Individuals with AF may be symptomatic or asymptomatic (silent AF). Common symptoms of AF include palpitations, fatigue, dizziness, dyspnea, chest pain and weakness. Silent AF is common, however, as one-third of patients with AF do not have any symptoms at all (33). The incidence and prevalence of AF may be substantially underestimated due to silent AF (34). The consequences are the same as that of symptomatic AF (5, 35). Similar to AF, atrial flutter (AFL) is a common abnormal heart rhythm in which the heart beats fast but in a regular pattern or rhythm. AFL is usually symptomatic and its ECG characteristics include negative flutter waves in II, III and aVF and positive flutter waves in V1 or positive flutter waves in lead II, III, aVF and the P-waves have a notch on the apex (36).

AF is frequently associated with other cardiac diseases such as coronary heart disease (CHD), valvular heart disease, heart failure and comorbidities such as hypertension, type 2 diabetes, heart failure, chronic obstructive pulmonary disease,

hyperthyroidism, obstructive sleep apnea, renal failure, stroke and cognitive disturbance (2, 16, 37). LA enlargement and left ventricular hypertrophy (LVH) is also associated with an increase in the risk of AF (16, 17, 38).

1.3.1 Atrial fibrillation and stroke

Stroke can happen at any time when brain cells are deprived of oxygen and begin to die (39). It was ranked as the second most common cause of death and the third most common cause of disability-adjusted life years (DALYs) worldwide in 2010 (40). In Norway, stroke was the third most common cause of death among deaths from cardiovascular diseases in 2016 (41). AF is associated with a four- to fivefold increased risk of stroke (42-44). However, several studies have yielded conflicting results regarding the relation between types of AF and risk of stroke (44). Some studies have reported a higher rate of stroke among those with permanent AF compared with paroxysmal AF (45-49), while other studies did not report any significant difference (50-60). The conflicting result might be due to methodological issues such as small sample size with limited number of events, confounding or due to differences in use of anticoagulation in patients with paroxysmal or permanent AF (44). However, this difference might also be because the pathophysiological change or abnormalities that occur are present continuously in patients with permanent AF, but only intermittently in patients with paroxysmal AF (44). Different studies have found higher risk for ischemic stroke among those with AF compared to those with AFL (61, 62).

The pathophysiology of stroke caused by AF implicates stasis and thrombus formation in a structurally abnormal and dilated atrium (34). The presence of AF increases the stroke severity such as hemorrhagic transformation (63). The risk of

stroke in AF patients depends upon the co-existence of other factors in patients with AF. Increasing age, male sex, hypertension, diabetes mellitus, valvular heart disease, inflammatory disorders, sleep apnea and tobacco use are considered risk factors for both AF and stroke (34, 64).

1.3.2 CHA_2DS_2-VASc score

The CHA_2DS_2-VASc risk score is a multifactorial tool, which stratifies stroke risk in the AF patient. This stratification scheme helps clinicians to make decisions on anticoagulant treatment (65). The new risk factor based scheme is expressed as an acronym, CHA_2DS_2-VASc, denoting congestive heart failure, hypertension, age 65-74 or age $\geq$ 75, diabetes, stroke, vascular disease, and sex (female). Two points are given for age $\geq$ 75 and stroke, transient ischaemic attack or thromboembolism, whereas one point is given for other risk factors. Patients with a CHA_2DS_2-VASc risk score of 2 or more in men and women (less than 65 years), and 3 or more in women 65 years and older, have been proved to benefit from oral anticoagulants (5). This risk stratification technique is important as it not only identifies those at high risk of stroke, but also patients who remain at low risk without need for anticoagulants (65).

1.3.3 Atrial fibrillation and cognitive function

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, with essentially preserved functional abilities (66). Dementia is a condition, which occurs when acquired cognitive impairment has become severe enough to compromise social or occupational functioning (66). Based on estimates from 2005, 24 million people have dementia and this number will double every 20 years provided there is no change in mortality or effective preventive strategies or no curative treatments are available (67). Prevalence of dementia increases exponentially

with age and doubles every five years after age 65 and the incidence increases steadily until age 85 or 90, and then continue to rise but less rapidly (66). However, such an analysis will exaggerate the prevalence of dementia as it is based on an analysis extrapolating the current age-specific prevalence on the large number of elderly as life expectancy increases. A recent study of dementia prevalence in England and Wales incorporating the falling incidence (2.7% annual decline), estimates 25% increase in dementia prevalence from 2015-2025. The increase in dementia prevalence is due to population ageing rather than the increase in the prevalence (68). The prevalence and incidence of MCI will differ depending on how MCI is defined (69). Cognitive impairment and dementia is thus one of the major public health problems worldwide.

Age, genetic factors, cardiovascular disease, sleep apnea, head injury, lifestyle (smoking and heavy alcohol consumption) and environment (pesticides exposure) can all influence the occurrence of cognitive impairment and dementia (66). Several studies have suggested AF as a risk factor for cognitive decline and dementia (70-72). A meta-analysis including four cross-sectional and six prospective studies confirmed this association, independent of stroke history (73). The association between AF and cognitive decline is highly dependent on the characteristics of the population having AF. The association may not be directly related to AF but could be due to an aging cohort with multiple comorbidities. One mechanism for cognitive decline due to AF might be silent cerebral infarcts. This was shown in the ARIC Study (1993-2006) where 935 stroke-free participants had larger annual decline in the cognitive test as shown by symbol substitution test among participants with AF compared to participants without AF. However, this association was present only in participants in whom prevalent or incident cerebral infarcts were detected on brain magnetic

resonance imaging (74). Other mechanisms, which explain this association, could be microemboli, microbleedings and cerebral hypoperfusion (75-77).

2. Aims of the thesis

The general objective of this thesis was to study echocardiographic risk factors for AF and complications of AF with emphasis on stroke and cognitive function in a longitudinal study of a large general population.

The specific aims were:

1. To investigate the association between diastolic dysfunction and risk of incident clinical AF in the population-based Tromsø Study with 16 years of follow-up.

2. To investigate the predictive ability of combinations of CHA_2DS_2-VASc score, LA size and AF status for odds of incident stroke in the population-based Tromsø Study with 18 years of follow-up.

3. To investigate the association between AF and change in cognitive function in the population-based Tromsø Study with 6 years of follow-up of stroke-free subjects and to study whether known stroke risk factors modulate this association.

3. Material and Methods

3.1 Study population: The Tromsø Study

The Tromsø Study is a prospective cohort study with a mainly Caucasian population, conducted in the municipality of Tromsø, North Norway (78). It was initiated in 1974 with the emphasis on epidemiology of, and surveillance of modifiable risk factors for, cardiovascular diseases. Cardiovascular mortality was very high at that time in Norway, especially in North Norway. The study has expanded its horizon and now includes many different diseases and health aspects. It includes seven surveys (1974 to 2016) referred to as Tromsø 1-Tromsø 7 to which total birth cohorts and representative population samples have been invited. A second extended sub-sample screening was also included in all surveys since Tromsø 4. These are referred to as Tromsø 4-Tromsø 7 visit 2. In the visit 2, participants of certain age groups and some random participants were invited. The study includes questionnaire data, biological specimen's collection and clinical measurements. It is a longitudinal study with repeated measurements performed at a regular interval in the same individuals, as well as including new participants. The study has been approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health and complies with the declaration of Helsinki. The participants have signed a written informed consent from Tromsø 4 and onwards.

The self-administered questionnaires contain a wide range of information about different diseases and symptoms, medication, lifestyle aspects, socioeconomic status and family history of diseases.

The physical examination consists of several measurements such as heart rate, blood pressure, height and weight. The later surveys from Tromsø 4 also include other

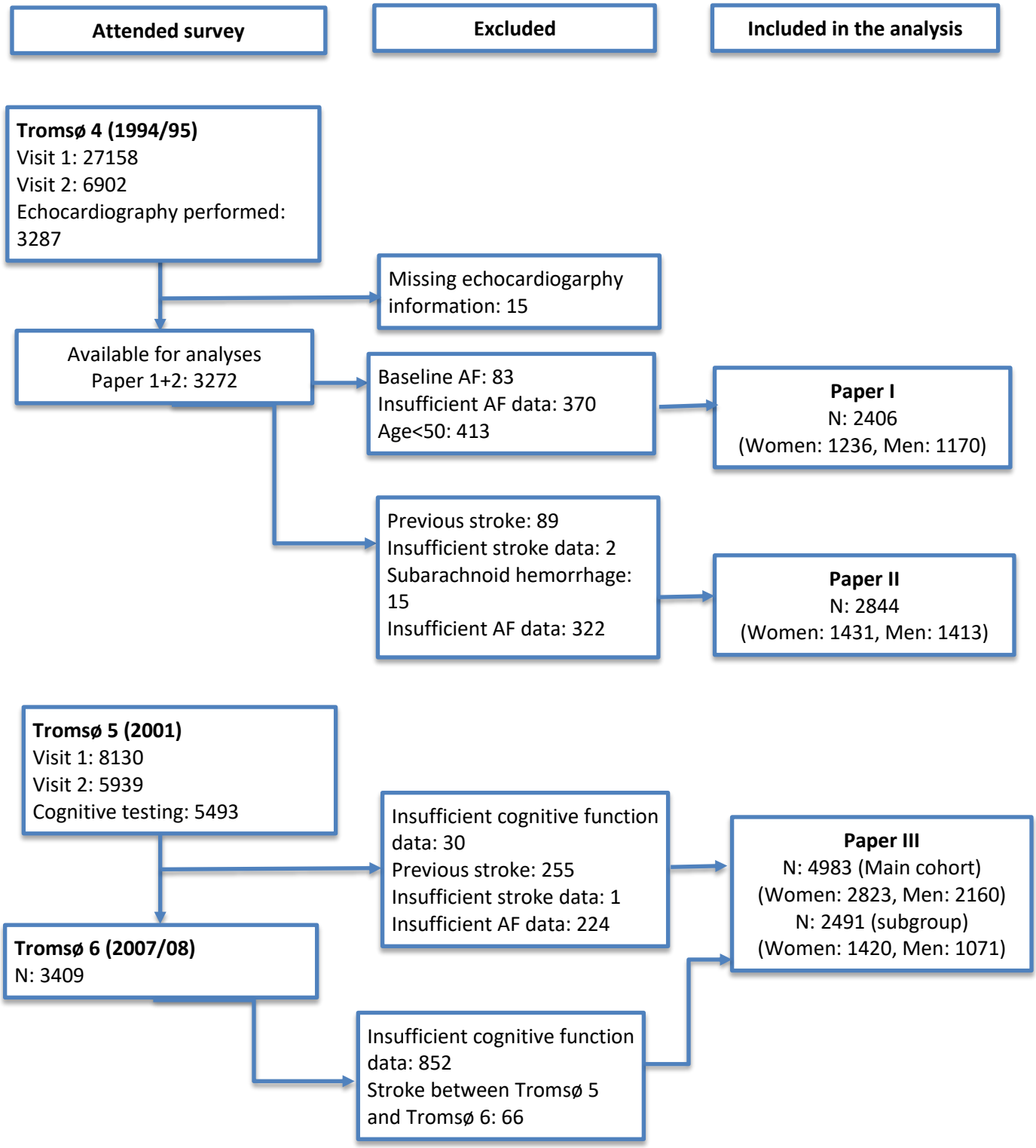
physical examinations such as echocardiography. Cognitive testing was included from Tromsø 5 and onwards. Blood samples of the participants are analyzed for different measurements including non-fasting serum total cholesterol, high-density lipoprotein cholesterol and creatinine. The papers included in this thesis are based on data from Tromsø 4 (paper I and paper II), Tromsø 5 and Tromsø 6 (paper III). An overview of the study population is given in the flowchart (Figure 2).

Tromsø 4 was performed in 1994-95 in which all inhabitants 25 years or older were invited and 27158 (77%) of the eligible population participated. Among them, all the participants between the age 55-74 years and 5-10% from the other age group (aged 25-54 years and 75-84 years) were invited for the extensive additional examination in visit 2. The 6902 (88%) of the individuals who attended were randomly allocated to one of two lines of examinations, one of which comprised echocardiographic examinations. This group constitutes the study population for paper I and paper II.

In paper I, after exclusion of participants without informed consent, with no echocardiography performed, with baseline AF, insufficient AF data and those that were less than 50 years of age, 2406 participants (1236 women and 1170 men) were included in the study.

In paper II, after exclusion of those without informed consent, with no echocardiography performed, with baseline stroke, insufficient AF data and stroke data and with subarachnoid hemorrhage, 2844 (1431 women and 1413 men) participants were included in the study.

Figure 2: Flowchart of the study population. The Tromsø Study



Tromsø 5 was conducted in 2001 and 8130 (79%) participants aged between 30 and 89 years participated. All inhabitants who attended both visits of Tromsø 4 were invited to the Tromsø 5 visit 2, and 5939 (85%) attended. Cognitive testing was performed in 5493 participants; the test was not performed in 446 subjects due to logistic reasons.

Tromsø 6 was conducted in 2007-08, a total of 12984 (66%) women and men aged between 30 and 87 years participated. For the Tromsø 6 visit 2, all inhabitants who participated in the Tromsø 4 visit 2, individuals aged 50-62 years or 75-84 years and a 20% random sample of those between 63-74 years were invited. The cognitive tests in both Tromsø 5 and Tromsø 6 were attended by 2737 participants. This group constitutes the study population for paper III.

In paper III after exclusion of those with previous stroke and insufficient stroke, AF and cognitive function data, 2491 (1420 women and 1071 men) participants were included in the study.

3.2 Data collection and ascertainment of endpoints

Self-administered questionnaires were provided to collect information on baseline characteristics. From the questionnaires, we used data on education level, alcohol intake (no alcohol/low alcohol intake (0–4 times/month)/high alcohol intake (≥5 times/month)) and coffee consumption (cups/day), smoking (current/previous/never), diabetes (yes/no), antihypertensive treatment (current/previous/never), depression (yes/no), palpitations (yes/no), prevalent cardiovascular diseases (CHD) (yes/no), thyroid disease (yes/no) and physical activity level. Education level was categorized as primary and secondary school (0-9 years), upper secondary school (10-12 years), college/university <4 years and

college/university ≥4 years. Physical activity level was categorized as physically active (weekly exercise with sweating or being out of breath or ≥3 hours per week of light exercise without sweating or being out of breath) or physically inactive (<3 hours per week of activity without sweating or being out of breath).

Physical examinations was performed with measurements of height, weight, blood pressure and heart rate. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and body surface area (BSA) was calculated by Du Bois formula ((Weight$^{0.425}$×Height$^{0.725}$)×0.007184). Blood pressure and heart rate were measured three times with one-minute intervals after 2 minutes resting, and the mean from the second and third reading was used in the analyses. The blood pressure measurements were performed with an automatic device (Dinamap Vital Signs Monitor 1846, Citrikon). We defined hypertension as systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or current use of antihypertensive medication.

From the blood sample analysis, we used information about blood lipids (total cholesterol and HDL-cholesterol) and plasma creatinine.

Incident clinical AF was documented by an electrocardiogram (ECG). All AF cases were obtained from the hospital diagnosis registry at the University Hospital of North Norway (outpatient clinic included) which is the only hospital in this area. Norway has a unique national 11-digit identification number that allows linkage to diagnosis registries. The identification numbers of the participants were linked to the diagnosis registry at the hospital and to the National Causes of Death Registry at Statistics Norway, using the following diagnostic codes: ICD-9 codes 427.0-427.99 and ICD-10 codes I47 and I48. Paper versions of hospital records (used until 2001) were manually

searched for notes on AF and text searches with the term ‘atrial fibrillation’ were performed in the electric records for participants with diagnosis of cerebrovascular or cardiovascular events but without diagnosis of arrhythmia. An independent endpoint committee adjudicated hospitalized and out-of-hospital events. Participants with transient AF occurring only during acute myocardial infarction (MI) or cardiac surgery and those with AF documented only in the terminal phase of life (last week) were not classified as AF. All AF cases (paroxysmal, persistent or permanent) were merged in the analyses.

All stroke cases were also obtained from the hospital diagnosis registry and linkage was done through the national identification number. The identification numbers of the participants were linked to the diagnosis registry at the hospital and to the National Causes of Death Registry at Statistics Norway. Possible cases of fatal and non-fatal stroke were identified by the following diagnostic codes of cerebrovascular disease: ICD 8 and 9 codes 430-438, and ICD 10 codes I60-I69. In addition, systematic manual and electronic search were performed in the medical records for patients with ICD 8 and 9 codes 410-414 and 798-799, and ICD 10 codes I20-I25 and R96, R98 and R99. An independent endpoint committee adjudicated hospitalized and out-of-hospital events. We merged all types of stroke, but excluded subarachnoid hemorrhage from our analysis.

3.3 CHA_2DS_2-VASc score

We calculated CHA_2DS_2-VASc score for paper II and paper III with a slight modification from the previous guidelines, and several others supports this new guideline (5, 79). The CHA_2DS_2-VASc scoring system as used in our papers is presented in Table 1.

Table 1. CHA_2DS_2-VASc scoring system

CHA_2DS_2-VASc	**Score**		**Comment**
	Guidelines	Paper II and III	
Congestive heart failure	1	1	
Hypertension	1	1	
Age $\geq$ 75 years	2	2	
Diabetes mellitus	1	1	
Stroke/transient ischemic attack/ thromboembolism	2	0	Stroke is an endpoint in paper II and only stroke free participants were included in paper III
Vascular disease	1	1	
Age 65-74 years	1	1	
Sex category (Female)	1 ($\geq$ 65 years age)	1 ($\geq$ 65 years age)	

3.4 Echocardiographic examination

Echocardiographic examination was performed by one physician and two expert cardiologists using a VingMED CFM 750 (VingMed Sound A/S, Horten, Norway) with a combined 3.25 MHz mechanical and 2.5 MHz Doppler probe, using the standard apical and parasternal long and short axis views. Standard 2D-guided M-mode registration of LA size, internal dimensions of the LV and wall thickness of the septum and posterior wall were made from leading edge to leading edge convention. The measurement of peak flow velocity in E-wave, A-wave, peak E/A ratio and EDT were done on-line in one heart cycle. Heart rate influence was minimized by measuring EDT as the time between the peak E-wave and the upper deceleration slope extrapolated to the zero baselines.

For the analysis, LA size was indexed by BSA, valvular heart disease was defined as mitral insufficiency grade 3 (>7 cm^2), heart failure as left ventricular ejection fraction (LVEF) <0.5 and hypertrophy as LV posterior wall end diastole M-mode > 1.4 cm and/or interventricular septum end diastole M-mode >1.4 cm.

LA size and mitral Doppler indices were used for evaluating diastolic dysfunction in paper I. The classification was done according to current guidelines and previously published data and is presented in Table 2 (80, 81).

Table 2. Classification of diastolic dysfunction according to LA size and mitral Doppler indices

Index	**Normal values**	**Diastolic dysfunction paper I**
E/A ratio	0.75-1.5	<0.75 or >1.5
EDT	≥140 ms	<140 ms
LA size	<2.2 cm/m^2	Moderately enlarged 2.2-2.79 cm/m^2 or severely enlarged ≥2.8 cm/m^2

E/A ratio, E-wave/A-wave ratio; EDT, E-wave deceleration time; LA, left atrium

A reproducibility study was performed in a subsample of 58 participants by the two main cardiologists. The participants were examined twice with a one-week interval. Both observers examined each subject without change of position at each examination. Measurement pairs of Doppler registrations were done in all subjects, but only 40 subjects had measurement pairs of M-mode registrations (82).

3.5 Cognitive testing

Cognitive function was assessed by three standardized tests, chosen by a group of neuropsychologists and epidemiologists for use in Tromsø 5. The tests were chosen based on their ability to detect early cognitive decline and their feasibility as

screening tests in an epidemiological setting with a large number of participants (83, 84).

The twelve-word memory test is a test of short time verbal memory with immediate free recall of 12 nouns that were shown written on a board. Each noun were pronounced one at a time with a 5-seconds interval (84). The participants then had two minutes to recall the words. One point was given for each word correctly recalled, giving the range from 0 to 12 points.

The digit-symbol coding test is part of the Wechsler adult intelligence scale (WAIS) and is used to examine psychomotor speed, attention, and mental flexibility (85). This test consists of rows containing small blank squares, each paired with a randomly assigned number from one to nine. Above these rows there was a printed key that paired each number with a different nonsense symbol. Following a practice trial on the first seven squares, the subjects were asked to consecutively fill in as many as possible of the blank spaces with the corresponding symbol over 90 seconds. Subjects were encouraged to perform the task as quickly and accurately as possibly.

The tapping test is a test mainly of psychomotor tempo. The subjects were asked to tap as many times as possibly in 10 seconds with their index finger. The taps were performed on a computer, which registered the number of taps. The task was repeated four times on both dominant hand and non-dominant hand. The mean of the average number of the three last taps on each hand was used in the analyses (85).

3.6 Statistical analyses

The STATA statistical software package was used for all the analyses. Analysis for paper I and paper II was performed using version 12, while version 14 was used for

the analysis in paper III. Baseline characteristics were presented as means and standard deviation (SDs) for continuous variables or numbers and proportions of group total for categorical variable. Differences between groups were assessed by t-tests, chi-square tests and Fisher´s exact test and linear trends across quartiles were tested using linear regression for continuous variables and logistic regression for binary variables.

In paper I, sex-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for AF were estimated by multivariable Cox proportional hazard regression models. Interaction was checked between the main independent variables (atrial size, mitral Doppler indices group) and sex. Colinearity was tested with all the variables and those with colinearity (tolerance <0.10) were excluded from the final model. Categorical variables with very few cases (<7%) in each category (CHD, valvular heart disease, hypertrophy and heart failure) were also excluded from the final model. C-statistic of the model was calculated to predict its clinical usefulness for distinguishing high-risk from low-risk subjects and log-likelihood ratio test to evaluate whether addition of another variable improved the predictive ability significantly. The proportional hazard assumption was validated with visual inspection of log-minus-log plots of the survival curves.

In paper II, odds ratios (ORs) for stroke were estimated using both age-adjusted and multivariable logistic regression analysis. Interaction was checked between LA size and AF and sex. C-statistic of the model was calculated. In addition, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated to quantify improvement in model performance. A user written program by Liisa Byberg was used to calculate the NRI and IDI.

In paper III, the mean cognitive score in Tromsø 5 was estimated according to age groups, AF status and LA size (grouped) adjusted for age, sex and length of education. The mean change in cognitive test scores from Tromsø 5 to Tromsø 6 was estimated with multivariable linear regression analysis. Interaction was checked between age and AF, and sex and AF, for change in cognitive test scores and for the CHA_2DS_2-VASc score, AF and LA size with sex and length of education for each cognitive test. The model assumptions were confirmed by graphical inspection of residuals. A two-sided $p<0.05$ was considered statistically significant in all three papers.

4. Results

4.1 Paper I: "Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010"

In this paper, we studied the association between diastolic dysfunction and AF with 16 years of follow-up. The study population for this paper were participants from Tromsø 4 cohort, who attended visit 2 and were subject to echocardiography (n=2406). The mean age of the participants was 63 years, and 16% women and 23% men developed AF during follow-up.

LA size and mitral Doppler indices were used for evaluating diastolic dysfunction in this paper. The risk of AF increased with increasing LA size. In multivariable Cox proportional hazards regression analysis adjusted for age, sex, height, BMI, hypertension, diabetes and palpitation, a moderately enlarged LA was associated with 1.6 (95% CI: 1.2 to 2.0) increased risk of AF compared with subjects with normal LA size. In subjects with severely enlarged LA size, HR for AF was 4.2 (95% CI: 2.7 to 6.5) compared with subjects with normal LA size. The adjustment for mitral Doppler

indices did not change the result. No association was found between AF and mitral Doppler indices, but when LA size was also adjusted for, abnormal mitral Doppler flow was associated with 1.3 (95% CI: 1.0-1.6) increased risk of AF compared with subjects with normal mitral Doppler flow. When we combined information concerning LA size and mitral Doppler flow, we found that in subjects with severely enlarged LA and abnormal mitral Doppler flow, HR for AF was 3.7 (95% CI: 1.6 to 8.7) compared with those with normal LA size and mitral Doppler flow. The AF risk was slightly decreased in women with severely enlarged left atria when those with coronary heart disease, valvular heart disease, heart failure or hypertrophy were excluded. However, we have not adjusted for these in the multivariate analysis due to very few cases in each category.

4.2 Paper II: "CHA_2DS_2-VASc score, left atrial size and atrial fibrillation as stroke risk factors in the Tromsø Study"

In this paper, we aimed to investigate the predictive ability of combinations of CHA_2DS_2-VASc score, LA size and AF status for odds of incident stroke with 18 years of follow-up. The study populations for this paper were participants from Tromsø 4 who attended visit 2 and were subject to echocardiography (n=2844). The mean age of the participants was 59 years. Incident stroke was identified in 10.1% women and 12.7% men.

Participants with CHA_2DS_2-VASc $\geq$1 and LA size <2.8 had about 4 times (95% CI: 2.6 to 5.3) increased odds of stroke, whereas participants with CHA_2DS_2-VASc $\geq$1 and LA size $\geq$2.8 had about 9 (95% CI: 5.3 to 16.4) times increased odds of stroke compared with participants with CHA_2DS_2-VASc score 0, irrespective of AF status.

There was minimal impact on the OR estimates when significant covariates were adjusted for.

We also performed the analysis including eight participants with AF in the terminal 7 days of life, where three died from stroke and the result was unchanged. The point estimates remained unchanged when palpitations were also adjusted for. Palpitations were not an independent predictor of stroke and the stroke incidence was similar among those with or without palpitations.

4.3 Paper III: "Atrial fibrillation is associated with cognitive decline in stroke-free subjects: The Tromsø Study"

In this paper, we studied the association between AF and cognitive decline in stroke-free subjects with 6 years of follow-up. The study participants for this study were for the cross-sectional analysis subjects (n= 4983) who attended Tromsø 5 visit 2 and were subject to cognitive testing and for the longitudinal analysis (n= 2491) those who had data concerning cognitive testing from both Tromsø 5 and Tromsø 6. The mean age of the participants was 65.4 years.

The main outcome of this study was change in cognitive score from Tromsø 5 to Tromsø 6, measured by the verbal memory test, the digit-symbol coding test and the tapping test. The mean reduction in the tapping test scores was significantly larger in participants with AF (5.3 taps/10 sec; 95% CI: 3.9, 6.7) compared with those without AF (3.8 taps/10 sec; 95% CI: 3.5, 4.1). The adjustment for risk factors did not change the estimates and were similar for both sexes.

We also added depression and physical activity level as covariates in the multivariable model, which did not change the result in this subpopulation. Also, the

adjustment for LA size among subjects with echocardiography performed had no effect. No association was found with change in the digit-symbol coding test and the verbal memory test.

5. Discussion

The discussion section has been divided into two parts. In the first part, the discussion of the main results in the paper will be done in accordance with previously existing research. In the second part, the consideration and limitations of methods used in the papers will be discussed.

5.1 Discussion of main results

Our main findings was that enlarged LA size as a measure for diastolic dysfunction was a risk factor for AF. Enlarged LA and CHA_2DS_2-VASc score $\geq$1was a strong predictor for stroke, regardless of AF status, and repeated cognitive screening found AF as a risk factor for cognitive decline measured as declining tapping test performance.

5.1.1 Atrial fibrillation and diastolic dysfunction

We used LA size and mitral Doppler indices as measures for evaluating diastolic dysfunction. When adjusted for other risk factors, we found that the risk of AF increased with increasing LA size. This is in line with some previous studies, which have found higher risk of AF among those with larger LA (24-27, 29, 86, 87). The cross-sectional ARIC study also found higher prevalence of AF among those with dilated LA (88). The LA enlargement is an expression of pathology, as LA size does not change with ageing (28). The enlargement is due to the change in filling dynamics associated with abnormal LV relaxation, which decreases passive emptying volume

from the LA to the LV and decreased direct flow volume from pulmonary veins into the LV in early diastole. To compensate, active LA contraction is enhanced, increasing the active emptying volume in late diastole, which preserves LV stroke volume, but it also enlarges the LA (29). LV diastolic dysfunction as a predictor for AF was found in one other study among subjects aged 65 years and older, and also confirmed by the Framingham Study among people with mean age of 75 years (25, 89).

Increased risk of AF among those with diastolic dysfunction was also found among patients with acute MI and reduced LV systolic function (30). We did not find any independent association between increasing degree of diastolic dysfunction based on mitral Doppler indices and AF, which is in contrast to the study from Minnesota among participants age 65 years or older. In this study, ECG results performed among participants between 1990 and 1998 were reviewed and a positive association was found between mitral Doppler indices and risk of AF (25). The difference in the findings from our study could be due to difference in the age of the participants as our study was performed among subjects aged 50 years or older while the other studies have older participants. As compared to older people, the classification of diastolic dysfunction may be less precise among middle age groups as the E/A ratio is high and DT is low in young or middle-aged adults (20, 90).

We found increased risk of AF among subjects when abnormal diastolic flow was combined with enlarged LA, which has also been shown in a previous study (23). Among LA size and mitral Doppler indices, LA size provides a long term view as it is independent of loading condition whereas mitral Doppler indices reflects only a snapshot which can change if the loading condition changes. LA size or mitral

Doppler indices as a measure for diastolic dysfunction has been shown as a risk factor by many studies as mentioned previously. Our study provide further evidence that addition of this combination model (LA size and mitral Doppler indices) to a number of sociodemographic variables and cardiovascular risk factors increased the ability to predict AF occurrence (91).

Generally, women have reduced ventricular wall thickness and smaller LA compared to men, which explains the reason for lower prevalence of AF among women (92). The cross-sectional ARIC study found that women more than men with dilated LA had stronger risk for AF than those with normal LA size (88). We did not perform sex-specific analysis combining mitral Doppler flow and LA size due to few cases of AF in each category. However, we performed sex-specific analysis according to LA size and found that HRs for AF according to LA size had similar associations in both sexes.

5.1.2. Atrial fibrillation and stroke

AF is an established risk factor for stroke and the association has previously been shown by many studies (43, 44, 93). Different studies have also shown various strength of the association depending on types of AF and stroke in different population (45-49). The other studies have suggested that AF is not a sufficient risk factor for stroke by itself, but rather the risk of stroke depends on co-existence of other risk factors in patients with AF (34). Thus, we wanted to investigate the predictive ability of combinations of CHA_2DS_2-VASc score, LA size and AF status for the odds of incident stroke. We found that adding LA size to elevated CHA_2DS_2-VASc score gave a better stratification of stroke risk irrespective of AF status. To the best of our knowledge, no other studies have combined these factors to identify stroke

risk, but have assessed the association with stroke risk for each factor separately. In a previous study from the Tromsø Study, palpitations were found as a strong risk factor for AF (94), but adding palpitations to our model did not change the point estimate for stroke risk in those with enlarged atria but without detected AF.

A prospective study among non-AF, high-risk patients found that CHA_2DS_2-VASc score strongly predicts new onset of ischemic stroke including other cardiovascular endpoints (95). Another prospective study performed among heart failure patient found CHA_2DS_2-VASc score associated with the risk of ischemic stroke irrespective of AF status (96). Several studies have found that LA size is associated with AF and stroke (26, 97-99). Among these studies, a study in a Chinese population without AF found an association between increased LA size and incident stroke only in women (97). In contrast, the Framingham Heart Study found LA enlargement as a significant predictor of stroke in men only, when adjusted for AF (98). We did not perform sex-specific analyses as no significant sex interaction was found with LA size in our cohort.

We found that among those with no known AF prior to stroke, the CHA_2DS_2-VASc score was a strong predictor and in this group 12.9% had AF diagnosed after the stroke. This is similar to a cross-sectional study of patients in national Swedish health registers, which found that the likelihood of AF among patients with stroke was directly correlated to the CHA_2DS_2-VASc score (100). We assume that the increased risk of stroke in participants with high CHA_2DS_2-VASc and no diagnosed AF is due to silent AF.

5.1.3 Atrial fibrillation and cognitive function

We found that AF was significantly associated with cognitive decline among stroke-free subjects as measured by the tapping test. Tapping test is an important test of cognitive function, as reduced motor speed is a sensitive marker of motor and cognitive cerebral dysfunction which includes reduced manual dexterity, coordination and global performance (101). Also, a study have shown that motor slowing as indicated by finger tapping speed preceded cognitive impairment (102). Earlier studies of cognitive function among stroke patients participating in the Tromsø Study have shown symbol coding and especially finger tapping to be very sensitive markers of dementia (103). We did not find any other study investigating the association between AF and cognitive decline using repeated measurements of tapping test. Our finding is in line with some other studies in stroke-free subjects (104, 105) and studies of men only (106, 107). These studies mainly used Mini Mental State Examination (MMSE) or other established diagnostic criteria for evaluating cognitive decline. Some longitudinal studies performed among high-risk groups (108) or elderly (109) also found similar result. In addition, some other longitudinal studies performed among participants with or without stroke history also found an association between AF and cognitive decline (110). A meta-analysis including four cross-sectional and six prospective studies confirmed this association, independent of stroke history (73). A retrospective registry study among AF patients have found higher risk of dementia in subjects without oral anticoagulant treatment (111). A cross-sectional study performed in a large general population of the region of Mainz, Germany found depression or depressive symptoms to be more frequent in participants with AF (112). In a longitudinal prospective study with follow-up at 12 and 36 months among participants aged over 60, no association was found between non-valvular AF and

cognitive decline (113). The difference in the findings could be because they did not include AF cases longer than 5 years or it might be because of the difference in neuropsychological tests employed. They used a comprehensive battery of neuropsychological tests, which lack certain features such as computerized tests, or they also used MMSE which is a much cruder screening tool and require a larger cognitive decline to be detected compared to the tests used in the Tromsø Study.

There was no change in the result when adjusted for other risk factors. When the CHA_2DS_2-VASc score was also included as its separate components, we found that age and sex were the main contributing factors of the score. A population cohort study found that the CHA_2DS_2-VASc score was a significant predictor of dementia among subjects with AF (114). The difference in findings could be because our study was among stroke free participants and only few had heart failure, vascular disease or diabetes. When LA size was added to our model, it did not affect the estimates. The power to detect the effect was low as only a subsample of 875 subjects had repeated measurements of LA size.

We performed sex specific analysis but did not present it as the sex-specific results were similar and no sex interaction was found. However, the Framingham Heart Study found men performing worse in some of the cognitive tests, while women performing better among those with AF (115). Similarly, another study from the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study) found men at more risk for cognitive impairment compared to women with AF (116).

5.2 Methodological considerations

Certain methodological considerations and limitations of our study are discussed in this section.

5.2.1 Study design

The Tromsø Study is a large population-based cohort study conducted in the Norwegian municipality of Tromsø (78). The major strength of this study is that it is conducted among representative samples from the general population. Further, the study is longitudinal, repeated at regular intervals of 6-7 years, and more than 15000 participants have attended three or more surveys. The Tromsø Study data is linked to the discharge diagnosis registry at the University Hospital of North Norway, the National Causes of Death Registry, and the population Register of Norway through a unique Norwegian personal identification number. This allows the investigator to follow the participants until the outcome of interest or end of follow-up.

In our analysis for paper I and paper II, all the information about risk factors are collected at baseline (Tromsø 4 1994-95) and the participants were followed until the date of outcome of interest or date of death, migration or end of follow-up at 2010 (paper I) and 2012 (paper II). In paper III, the baseline information including cognitive data were collected at Tromsø 5 (2001) following the participants for 6 years, the follow-up data about cognitive function was collected at Tromsø 6 (2007-08). We used data on AF status that was collected through 2008. The exclusion criteria for participants for each paper are described in the methods section.

The three standardized tests used for cognitive testing were chosen based on their ability to detect early cognitive decline and their feasibility as screening tests in an epidemiological setting with a large number of participants (85). However, these tests are restricted to the cognitive domains studied and might not give a total picture of the cognitive function. Mini-Mental State Examination was added in Tromsø 6, but we did not use this in our study, as follow-up data were not available.

The Tromsø Study does not acquire data on tissue Doppler recordings or mitral Doppler recordings during Valsalva Maneuver and also LA size is best evaluated with estimation of volume, but we could not use this, as such data was not available. The screening was done in 1994 on a single harmonic imaging machine (CFM 750 Vingmed (now GE)) which does not have a quality to justify quantification of volume. In the prospective CARDIA study LA diameter indexed by BSA or height performed equally to LA area with AUC of 0.77 and 0.78, respectively (117). Although LA diameter will not correctly represent the volume, LA diameter will detect the geometrical change from elongated atria in normal long axis to the cubic atria with enlargement due to increasing LV end diastolic pressure, mitral insufficiency, mitral stenosis or other causes of increased LA pressure, and thus will detect change from normal. The reproducibility study of echocardiographic data from Tromsø 4 found a non-significant mean (SD) intra-observer difference for LA diameter of 0.01 (±0.49) cm and a significant mean (SD) inter-observer difference of 0.16 (±0.34) cm (82). Another study comparing LA diameter and LA volume found LA diameter has higher interclass coefficients and lower precision compared to LA volume (118).

We have data concerning anticoagulant treatment at start of follow-up, but we do not know when the participants started on the treatment, when it was ended or changed during follow-up. This information could have been useful to know if the change in the treatment had any effect on the result.

5.2.2 Internal validity

The term internal validity refers to the result of the study being valid or true for the population being studied, and is threatened by bias and confounding (119). Bias is the

systematic error, which may occur during design or conduct of a study and can distort the true association in the study. There are different kinds of bias, which are often classified as selection bias and information bias.

Selection bias: The Tromsø Study ensures representative study participants with total birth cohorts and random samples of other age groups from the Tromsø municipality being selected and invited based on population registry (78). Selection bias may be present in this study as non-response bias. The attendance rate in Tromsø Study was relatively high (>75% in Tromsø 4 and 5) and 66% in Tromsø 6. The high attendance rate reduces the problem of selection bias. However, we cannot ignore that selection bias occurs due to differences between attendees and non-attendees. Participants who attended several surveys might be more concerned about their health and could therefore be healthier than the people who did not attended the surveys, or they may be older and sicker and are unable to attend. We could not perform any analysis among the non-attendees, as the Norwegian Data Inspectorate does not permit this. However, it was found that the age and sex adjusted mortality among subjects invited to Tromsø 4 was 6.9/1000 person-years in subjects who attended all Tromsø 2-4 surveys whereas it was 11.1/1000 person-years in subjects who were invited in all three, but only attended Tromsø 4. This shows that the participants who were consistent attendees had lower mortality compared to non-attendees (78). Difference between attendees and non-attendees has also been shown in other studies including the Tromsø Study mainly in demographic characteristics, prevalence of risk factors or disease and mortality (82, 120-122). The responders from the older age group were probably the mobile volunteers, which would limit the proportion of responders with present serious cardiovascular diseases.

In the Tromsø 4 visit 2, the subgroup with echocardiography performed had a lower proportion of women than those without. The educational level was lower among women. Thus, the subgroup with echocardiography performed had higher education level (82). We do not have information about the non-attendees in cognitive testing, but we assume some have cognitive decline and dementia both at baseline and follow-up. Although invited, institutionalized individuals might not be able to attend the sixth survey or to complete the questionnaire. In addition, 550 more participants completed the tapping test than the digit-symbol coding test and the proportion of subjects with cognitive impairment were higher among those who did not complete all tests.

In paper I, we excluded participants less than 50 years of age in our analysis for proper classification of diastolic dysfunction groups. EA-ratios and EDT was classified in four groups according to increasing degree of diastolic dysfunction (predictor of atrial fibrillation):

Group I (normal): EA ratio 0.75-1.5 and EDT > 140ms

Group II (Abnormal): EA ratio >1.5 and EDT > 140ms

Group III (Pseudo normal): EA ratio <0.75 and any EDT

Group IV (Restrictive): EA ratio >0.75 and EDT< 140ms

Studies have shown that there is decrease in E/A ratio and increase in EDT with advancing age (20, 90). Thus, this classification guideline does not hold true for younger age group. The younger age groups will not fit into the normal criteria even though they have normal diastolic dysfunction. However, the invitees for the Tromsø 4 visit 2 were those between age 55-74 years and only random 5% to 10% samples of the other age groups (aged 25-54 years and 75-84 years) which mean we have not

missed many cases. In addition, AF is not common among those less than 50 years of age.

Information bias and misclassification: Misclassification of AF could have occurred during this study. Although detailed search methods were used to detect AF cases (detailed description is given in the method section), there may still be many persons with silent AF. The true prevalence of silent AF is not well established and varies from 10% to 40% in various cohorts with higher prevalence in men and in older age groups (123). A study performed in a Norwegian general population cohort of 65 years and older with risk factors for stroke, identified previously undiagnosed AF in 0.9% of the population (7). In addition, subjects with the paroxysmal form of AF may fail to get their arrhythmia documented on an echocardiographic examination. Some AF patients are never hospitalized and some cases might have been missed this way. We also do not know if there is a difference between the groups that are referred and not referred to hospital.

Self-reported data were used in our papers to define some predictor variables. Generally, certain habits tend to be overreported (desired habits such as physical activity) and certain habits are underreported (less acceptable habits such as smoking or alcohol consumption). This could result in misclassification. Misclassification can be non-differential if the comparison is made between the longitudinal surveys, and if the questions are asked in the same way. However, the misclassification can be differential in respect to the outcome being measured.

Another bias is that of reproducibility of measuring techniques such as echocardiography. Reproducibility is the variation in measurements made on a subject under changing conditions (124). This may be a result of different measurement

methods or instrument being used, measurements being made by different observers or it may be due to measurements being made over a period, within which the error-free level of the variable could undergo non-negligible change (124). A reproducibility study of the echocardiographic data was performed in a subsample of 58 participants by two cardiologists. The participants were examined twice with one-week interval by both observers. The reproducibility study found no systematic measurement variability invalidating the data (90).

Confounding: This term refers to a situation in which a non-causal association between exposure and an outcome is observed as a result of the influence of a third variable or group of variables known as confounder (119). The most common example of confounders in the present study are age and sex. Unlike bias, confounding can be handled through statistical approaches such as stratification and regression models. In our analyses, we have adjusted for the confounding variables through methods based on multivariable regression models. The variables previously established as confounders were found through literature reviews and were adjusted for. The different confounders adjusted for in each paper have been described earlier. Confounding caused by some unknown factors could not be addressed.

5.2.3 External validity

External validity refers to the generalizability of the results, and whether they are also applicable to other populations. The criteria for participants in the Tromsø Study were age and residency in the largely urban municipality of Tromsø with enrollment based on the official population registry. There was a high attendance rate in the study and the endpoints were reliable. The majority of participants were of white, North-

European ancestry and there were very few immigrants. The results are thus probably applicable to other North-European populations.

6. Conclusions and implications for future research

The main conclusions are as following:

1. We found that enlarged LA as a measure for diastolic dysfunction was independently associated with an increased risk of AF, and adding measures of abnormal diastolic flow increased the predictive ability significantly. No association was seen between mitral Doppler indices alone and AF.

2. Our study also revealed that a combination of CHA_2DS_2-VASc score $\geq$1 and an enlarged LA is an important risk factor for stroke irrespective of AF status.

3. Using repeated standardized cognitive tests, we found that presence of AF was significantly associated with 40% greater cognitive decline as measured by the tapping test in stroke-free subjects of both sexes. The adjustment for other risk factors did not change the estimates.

A future pilot study with Holter monitoring in subjects with no known AF, but increased risk of AF and higher CHA_2DS_2-VASc score is recommended to check if they have silent paroxysmal AF. The feasibility and compliance in patients can be a problem. Thus, a pilot study can be performed first in a small high-risk sample from the general population. Further, it would be interesting to perform a linkage between data from the Tromsø Study and anticoagulation data from the National prescription database. Using the total sample will ensure enough power to detect changes in AF

risk of stroke when new anticoagulants instead of warfarin are introduced, as preliminary analysis in our echocardiographic subsample suggests.

Our study found enlarged LA size as a strong risk factor for AF and stroke, but did not find any relation to cognitive decline. As only a subsample had LA size measured the power to detect any impact on cognitive function was low. More participants with LA size data can be included in future studies in order to explore if a true association between LA size and cognitive function exists. The analysis of cognitive decline could be repeated with longer follow-up as data from Tromsø 7 (2015-16) has just recently been available for further validation.

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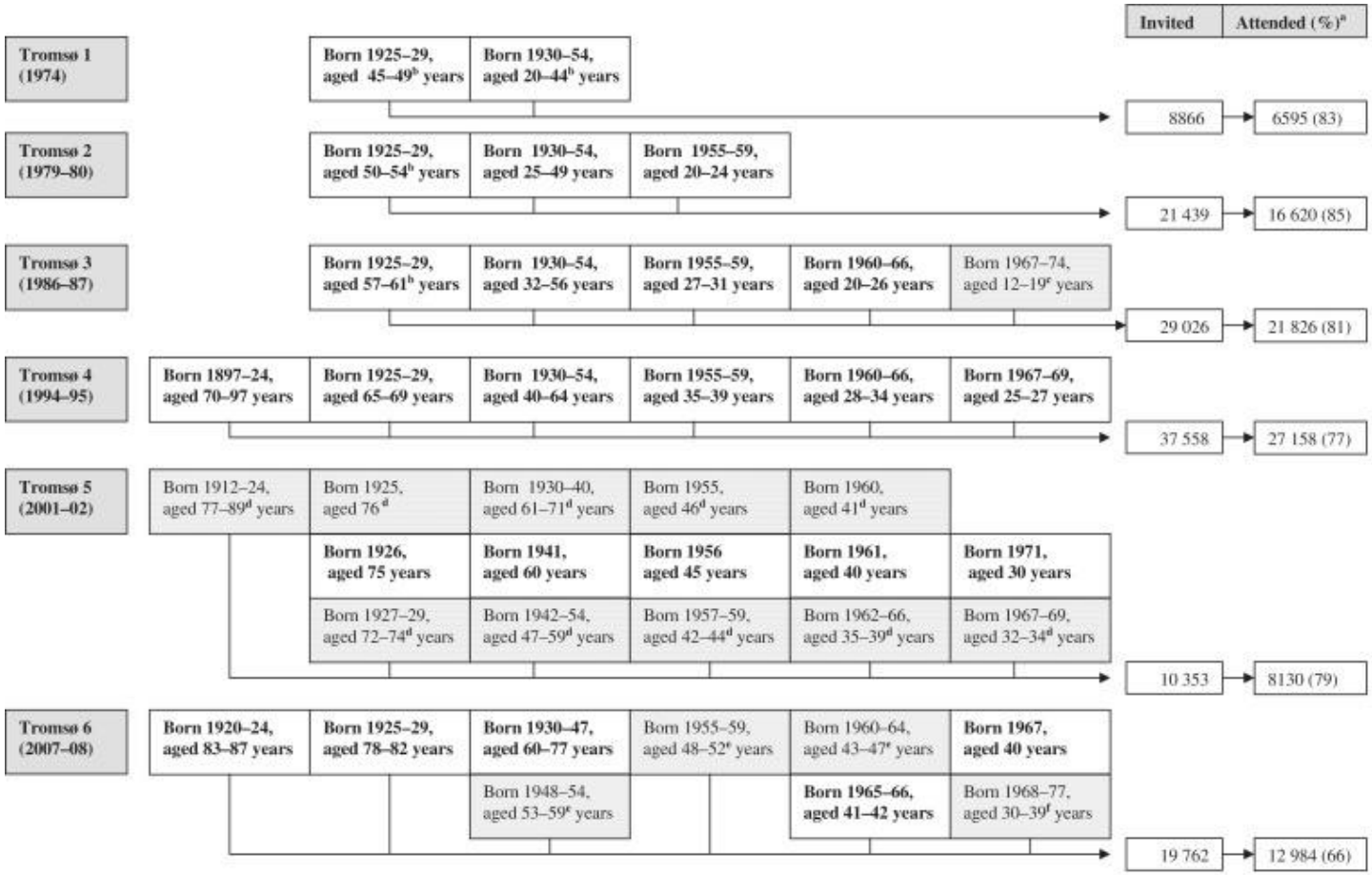
Paper I

Paper II

Paper III

Appendix 1

Figure: The Tromsø Study, cohort profile



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: 961-967.

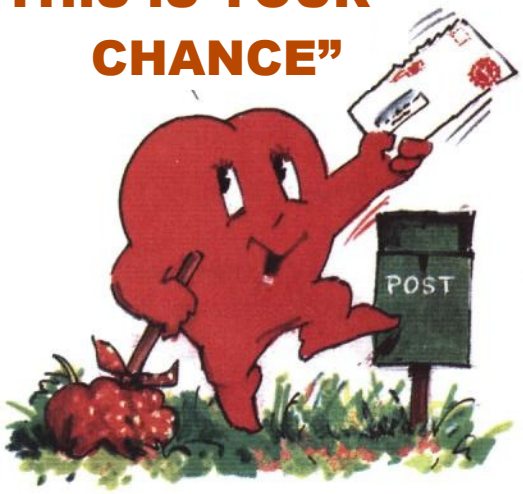
Appendix 2 a

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 2 b

2nd Questionnaire Tromsø 4

Visit 1, 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?	Yes	No
330	❑	❑

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

If you still menstruate or are pregnant: day/month/year

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

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

PREGNANCY

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

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

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

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 2 c

2nd Questionnaire Tromsø 4

Visit 1, 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	_____	_____

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

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

Appendix 3 a

Questionnaire Tromsø 5

Visit 1, persons < 70 years

Health survey

Personal Invitation

Don't write here

5.3 (Municipality) (County) (Country)

9.3 (Business) 9.4 (Occupation) 14.7 (Mark)

1. YOUR OWN HEALTH

1.1 What is your current state of health? *(Tick one only)*

Poor ☐ 1 | Not so good ☐ 2 | Good ☐ 3 | Very good ☐ 4

1.2 Do you have, or have you had?:

	Yes	No	Age first time
Asthma	☐	☐	
Hay fever	☐	☐	
Chronic bronchitis/emphysema	☐	☐	
Diabetes	☐	☐	
Osteoporosis	☐	☐	
Fibromyalgia/chronic pain syndrome	☐	☐	
Psychological problems for which you have sought help	☐	☐	
A heart attack	☐	☐	
Angina pectoris (heart cramp)	☐	☐	
Cerebral stroke/brain haemorrhage	☐	☐	

1.3 Have you noticed attacks of sudden changes in your pulse or heart rhythm in the last year? ☐ Yes ☐ No

1.4 Do you get pain or discomfort in the chest when:
Walking up hills, stairs or walking fast on level ground? ☐ Yes ☐ No

1.5 If you get such pain, do you usually:

Stop? ☐ 1 | Slow down? ☐ 2 | Carry on at the same pace? ☐ 3

1.6 If you stop, does the pain disappear within 10 minutes? ☐ Yes ☐ No

1.7 Can such pain occur even if you are at rest? ☐ Yes ☐ No

2. MUSCULAR AND SKELETAL COMPLAINTS

2.1 Have you suffered from pain and/or stiffness in muscles and joints during the last 4 weeks?
(Give duration only if you have had problems)

	No complaint	Some complaint	Severe complaint	Duration: Up to 2 weeks	Duration: 2 weeks or more
Neck/shoulders	☐	☐	☐	☐	☐
Arms, hands	☐	☐	☐	☐	☐
Upper part of your back...	☐	☐	☐	☐	☐
Lumbar region	☐	☐	☐	☐	☐
Hips, legs, feet	☐	☐	☐	☐	☐
Other places	☐	☐	☐	☐	☐
	1	2	3	1	2

2.2 Have you ever had:

	Yes	No	Age last time
Fracture in the wrist/forearm	☐	☐	
Hip fracture?	☐	☐	

3. OTHER COMPLAINTS

3.1 Below is a list of various problems. Have you experienced any of this during the last week (including today)?
(Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐
	1	2	3	4

4. USE OF HEALTH SERVICES

4.1 How many times in the last 12 months have you been to/used:
(Tick once for each line)

	None	1-3 times	4 or more
General practitioner (GP)	☐	☐	☐
Medical officer at work	☐	☐	☐
Psychologist or psychiatrist *(private or out-patient clinic)*	☐	☐	☐
Other specialist *(private or out-patient clinic)*	☐	☐	☐
Emergency GP *(private or public)*	☐	☐	☐
Hospital admission	☐	☐	☐
Home nursing care	☐	☐	☐
Physiotherapist	☐	☐	☐
Chiropractor	☐	☐	☐
Dentist	☐	☐	☐
Alternative practitioner	☐	☐	☐

5. CHILDHOOD/YOUTH AND AFFILIATION

5.1 How long altogether have you lived in the county? ☐☐ year
(Put 0 if less than half a year)

5.2 How long altogether have you lived in the municipality? ☐☐ year
(Put 0 if less than half a year)

5.3 Where did you live most of the time before the age of 16?
(Tick one option and specify)

Same municipality .... ☐ 1

Another municipality in the county ..... ☐ 2 Which one: _____

Another county in Norway ☐ 3 Which one: _____

Outside Norway ..... ☐ 4 Country:: _____

5.4 Have you moved within the last five years?

No ☐ 1 | Yes, one time ☐ 2 | Yes, more than once ☐ 3

6. BODY WEIGHT

6.1 Estimate your body weight when you were 25 years old: ☐☐☐ kg

7. FOOD AND BEVERAGES

7.1 How often do you usually eat these foods? *(Tick once per line)*

	Rarely /never	1-3 times /month	1-3 times /week	4-6 times /week	1-2 times /day	3 times or more /day
Fruit, berries	☐	☐	☐	☐	☐	☐
Cheese *(all types)*	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Boiled vegetables	☐	☐	☐	☐	☐	☐
Fresh vegetables/salad	☐	☐	☐	☐	☐	☐
Fatty fish *(e.g. salmon, trout, mackerel, herring)*	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.2 What type of fat do you usually use? *(Tick once per line)*

	Don't use	Butter	Hard margarine	Soft/light margarine	Oils	Other
On bread	☐	☐	☐	☐	☐	☐
For cooking	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.3 Do you use the following dietary supplements:

	Yes, daily	Sometimes	No
Cod liver oil, fish oil capsules	☐	☐	☐
Vitamins and/or mineral supplements?	☐	☐	☐

7.4 How much of the following do you usually drink? *(Tick once per line)*

	Rarely /never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 glasses or more /day
Full milk, full-fat curdled milk, yoghurt	☐	☐	☐	☐	☐
Semi-skimmed milk, semi-skimmed curdled milk,low-fat yoghurt	☐	☐	☐	☐	☐
Skimmed milk, skimmed curdled milk	☐	☐	☐	☐	☐
Extra semi-skimmed milk	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Water	☐	☐	☐	☐	☐
Mineral water (e.g. Farris, Ramløsa etc)	☐	☐	☐	☐	☐
Cola-containing soft drink	☐	☐	☐	☐	☐
Other soda/soft drink	☐	☐	☐	☐	☐
	1	2	3	4	5

7.5 Do you usually drink soft drink: with sugar ☐ 1 without sugar ☐ 2

7.6 How many cups of coffee and tea do you drink daily? *Number of cups*
(Put 0 for the types you don't drink daily)

Filtered coffee ..... ☐☐

Boiled coffee/coarsely ground coffee for brewing ..... ☐☐

Other type of coffee ..... ☐☐

Tea ..... ☐☐

7.7 Approximately how often have you during the last year consumed alcohol? *(Do not count low-alcohol and alcohol-free beer)*

Never consumed alcohol ☐ 1	Have not consumed alcohol last year ☐ 2	A few times last year ☐ 3	About 1 time a month ☐ 4
2-3 times per month ☐ 5	About1 time a week ☐ 6	2-3 times a week ☐ 7	4-7 times a week ☐ 8

To those who have consumed the last year:

7.8 When you drink alcohol, how many glasses or drinks do you normally drink? *number* ☐☐

7.9 Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours? *Number of times* ☐☐

7.10 When you drink, do you normally drink: *(Tick one or more)*

Beer ☐ Wine ☐ Spirits ☐

8. SMOKING

8.1 How many hours a day do you normally spend in smoke-filled rooms? *Number of total hours* ☐☐

	Yes	No
8.2 Did any of the adults smoke at home while you were growing up?	☐	☐
8.3 Do you currently, or did you previously live together with a daily smoker after your 20th birthday?	☐	☐

	Yes, now	Yes, previously	Never
8.4 Do you/did you smoke daily?	☐	☐	☐

If NEVER: Go to question 9 : (EDUCATION AND WORK)

8.5 If you smoke daily now, do you smoke:	Yes	No
Cigarettes?	☐	☐
Cigars/cigarillos?	☐	☐
A pipe?	☐	☐

8.6 If you previously smoked daily, how long is it since you quit? *Number of years* ☐☐

8.7 If you currently smoke, or have smoked previously:

How many cigarettes do you or did you normally smoke per day? *Number of cigarettes* ☐☐

How old were you when you began daily smoking? *Age in years* ☐☐

How many years in all have you smoked daily? *Number of years* ☐☐

9. EDUCATION AND WORK

9.1 How many years of education have you completed? *Number of years* ☐☐
(Include all the years you have attended school or studied)

9.2 Do you currently have paid work?

Yes, full-time ☐ 1 Yes, part-time ☐ 2 No ☐ 3

9.3 Describe the activity at the workplace where you had paid work for the longest period in the last 12 months. *(e.g. Accountancy firm, school, paediatric department, carpentry workshop, garage, bank, grocery store, etc.)*

Business: _____
If retired, enter the former business and occupation. Also applies to 9.4

9.4 Which occupation/title have or had you at this workplace? *(e.g. Secretary, teacher, industrial worker, nurse, carpenter, manager, salesman, driver, etc.)*

Occupation: _____

9.5 In your main occupation, do you work as self-employed, as an employee or family member without regular salary?

Self-employed ☐ Employee ☐ Family member ☐

	Yes	No
9.6 Do you believe that you are in danger of losing your current work or income within the next two years?	☐	☐

9.7 Do you receive any of the following benefits?	Yes	No
Sickness benefit (are on sick leave)	☐	☐
Old age pension, early retirement (AFP) or survivor pension	☐	☐
Rehabilitation/reintegration benefit	☐	☐
Disability pension (full or partial)	☐	☐
Unemployment benefits during unemployment	☐	☐
Social welfare benefits	☐	☐
Transition benefit for single parents	☐	☐

10. EXERCISE AND PHYSICAL ACTIVITY

10.1 How has your physical activity in leisure time been during this last year?
Think of a weekly average for the year.
Time spent going to work is count as leisure time. Answer both questions.

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

10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.
(Tick the most appropriate box)

Reading, watching TV or other sedentary activity? ..... ☐ 1

Walking, cycling or other forms of exercise at least 4 hours a week? ..... ☐ 2
(Include walking or cycling to work, Sunday walk/stroll,etc.)

Participation in recreational sports, heavy gardening, etc.? ☐ 3
(Note: duration of activity at least 4 hours a week)

Participation in hard training or sports competitions, regularly several times a week? ..... ☐ 4

11. FAMILY AND FRIENDS

11.1 Do you live with:

	Yes	No
Spouse/partner?.....	☐	☐

11.2 How many good friends do you have? *Number of friends* ☐☐

Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include other relatives.

11.3 How much interest do people show for what you do?
(Tick only once)

Great interest	Some interest	Little interest	No interest	Uncertain
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11.4 How many associations, sport clubs,groups, religious communities or similar do you take part in? *Number* ☐☐
(Write 0 if none)

11.5 Do you feel that you can influence what happening in your local community where you live? *(Tick only once)*

Yes, a lot	Yes, some	Yes, a little	No	Never tried
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

12. ILLNESS IN THE FAMILY

12.1 Have one or more of your parents or siblings had a heart attack (heart wound) or angina pectoris (heart cramp)? .....

Yes	No	Don't know
☐	☐	☐

12.2 Tick for the relatives who have or have had any of the illnesses: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Cerebral stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60 years	☐	☐	☐	☐	☐	☐
Asthma.....	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐

12.3 If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life):

Don't know, not applicable	Mother's age	Father's age	Brother's age	Sister's age	Child's age
☐	☐☐	☐☐	☐☐	☐☐	☐☐

13. USE OF MEDICINES

With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here.

13.1 Do you use:

	Now	Previously, but not now	Never used
Blood pressure lowering drugs	☐	☐	☐
Cholesterol-lowering drugs	☐	☐	☐

13.2 How often have you during the last 4 weeks used the following medicines?
(Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week but not daily	Daily
Painkillers non-prescription	☐	☐	☐	☐
Painkillers on prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐
Other prescription medicines ...	☐ 1	☐ 2	☐ 3	☐ 4

13.3 For those medicines you have checked in points 13.1 and 13.2, and that you've used during the last 4 weeks:

State the name and the reason that you are taking/have taken these (disease or symptom):
(Tick for each duration you have used the medicine)

Name of the medicine: *(one name per line)*	Reason for use of the medicine	How long have you used the medicine: Up to 1 year	1 year or more
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

If there is not enough space here, you may continue on a separate sheet that you attach

14. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

14.1 How old were you when you started menstruating? *Age in years* ☐☐

14.2 If you no longer menstruating, how old were you when you stopped menstruating? *Age in years* ☐☐

14.3 Are you pregnant at the moment?

Yes	No	Uncertain	Above fertile age
☐ 1	☐ 2	☐ 3	☐ 4

14.4 How many children have you given birth to? *Number of children* ☐☐

14.5 Do you use, or have you ever used?
(Tick once for each line)

	Now	Before, but not now	Never
Oral contraceptive pills/mini pill/ contraceptive injection	☐	☐	☐
Hormonal intrauterine device (IUD) *(not ordinary IUD)*..	☐	☐	☐
Estrogen *(tablets or patches)*	☐	☐	☐
Estrogen *(cream or suppositories)*	☐	☐	☐

14.6 If you use/have used prescription estrogen:
How long have you used it? *Number of years* ☐☐

14.7 If you use contraceptive pills, mini pill, contraceptive injection, hormonal IUD or estrogen, what brand do you use?

IE 050000 - 1042-1 - 24.000 - Beyer Hecos 02.01

Appendix 3 b

Questionnaire Tromsø 5

Visit 1, persons ≥ 70 years

E

Health survey

Personal invitation

Do not write here:

E13 (Municipality) (County) (Country) E15 (Mark)

E1. YOUR OWN HEALTH

What is your current state of health? *(Tick only once)*

Poor ☐ 1 | Not so good ☐ 2 | Good ☐ 3 | Very good ☐ 4

Do you have, or have you had?:

	Yes	No	Age first time
Asthma	☐	☐	
Chronic bronchitis/emphysema	☐	☐	
Diabetes	☐	☐	
Osteoporosis	☐	☐	
Fibromyalgia/chronic pain syndrome	☐	☐	
Psychological problems for which you have sought help	☐	☐	
A heart attack	☐	☐	
Angina pectoris (heart cramp)	☐	☐	
Cerebral stroke/brain haemorrhage	☐	☐	

	Yes	No
Do you get pain or discomfort in the chest when: Walking up hills, stairs, or walking fast on level ground?	☐	☐

If you get such pain, do you usually:

Stop? ☐ 1 | Slow down? ☐ 2 | Carry on at the same pace? ☐ 3

	Yes	No
If you stop, does the pain disappear within 10 minutes?	☐	☐
Can such pain occur even if you are at rest?	☐	☐

E2. ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had:

	Yes	No	Don't know
A heart attack (heart wounds) or angina pectoris (heart cramp)	☐	☐	☐

Tick for the relatives who have or have had any of the illnesses: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Cerebral stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60 years	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐

If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life)

Don't know, not applicable	Mother's age	Father's age	Brother's age	Sister's age	Child's age
☐					

E3. COMPLAINTS

Below is a list of various problems.
Have you experienced any of this during the last week (including today)?
(Tick once for each line)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future.	☐	☐	☐	☐
	1	2	3	4

E4. TEETH, MUSCLE AND SKELETON

How many teeth have you lost/extracted? *Number of teeth*
(disregard milk-teeth and wisdom teeth)

Have you been bothered by pain and/or stiffness in muscles and joints during the last 4 weeks?

	No complaint	Little complaint	Severe complaint
Neck / shoulders	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
Lumbar regions	☐	☐	☐
Hips, legs, feet	☐	☐	☐
Other places	☐	☐	☐

Have you ever had:

	Yes	No	Age last time
Fracture in wrist/forearm?	☐	☐	
Hip fracture?	☐	☐	

Have you fallen down during the last year? *(Tick once only)*

No ☐ 1 | Yes, 1-2 times ☐ 2 | Yes, more than 2 times ☐ 3

E5. EXERCISE AND PHYSICAL ACTIVITY

How has your physical activity been during this last year?
Think of a weekly average for the year.
Answer both questions.

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

E6. BODY WEIGHT

Estimate your body weight when you were 25 years old: kg.

E7. EDUCATION

How many years of education have you completed? *Number of years*

(include all the years you have attended school or studied)

E8. FOOD AND BEVERAGES

How often do you usually eat these foods?
(Tick once for each line)

	Rarely /never	1-3 times /month	1-3 times /week	4-6 times /week	1-2 times /day	3 times or more /day
Fruit, berries	☐	☐	☐	☐	☐	☐
Cheese (all types) ...	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Boiled vegetables ..	☐	☐	☐	☐	☐	☐
Fresh vegetables/salad	☐	☐	☐	☐	☐	☐
Fat fish (e.g. salmon, trout, mackerel, herring)	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

Do you use dietary supplements:

	Yes, daily	Sometimes	No
Cod liver oil, fish oil capsules	☐	☐	☐
Vitamins and/or mineral supplements ...	☐	☐	☐

How much of the following do you usually drink?
(Tick once for each line)

	Rarely /never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 glasses or more /day
Full milk, full-fat curdled milk, yoghurt	☐	☐	☐	☐	☐
Semi-skimmed milk, semi-skimmed curdled milk, low-fat yoghurt	☐	☐	☐	☐	☐
Skimmed milk, skimmed curdled milk	☐	☐	☐	☐	☐
Extra semi-skimmed milk	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Water	☐	☐	☐	☐	☐
Soft drink, mineral water	☐	☐	☐	☐	☐
	1	2	3	4	5

How many cups of coffee and tea do you drink daily?
(Put 0 for the types you do not drink daily) *Number of cups*

Filtered coffee .....

Boiled coffee/coarsely ground coffee for brewing .....

Other type of coffee .....

Tea .....

Approximately, how often have you during the last year consumed alcohol? *(Do not count low-alcohol and alcohol-free beer)*

Never consumed alcohol ☐ 1	Have not consumed alcohol last year ☐ 2	A few times last year ☐ 3	About 1 time a month ☐ 4
2-3 times per month ☐ 5	About 1 time a week ☐ 6	2-3 times a week ☐ 7	4-7 times a week ☐ 8

To those who have consumed the last year:

When you drink alcohol, how many glasses or drinks do you normally drink? *Number*

Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours? *Number of times*

E9. SMOKING

How many hours a day do you normally spend in smoke-filled rooms? *Number of total hours*

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

Do you currently, or did you previously live together with a daily smoker after your 20th birthday? ☐ Yes ☐ No

Do you/did you smoke daily? ..... ☐ Yes, now ☐ Yes, previously ☐ Never

If you have NEVER smoked daily;
Go to question E11 (BODILY FUNCTIONS AND SAFETY)

If you smoke daily now, do you smoke:

	Yes	No
Cigarettes?.....	☐	☐
Cigars/cigarillos?	☐	☐
A pipe?.....	☐	☐

If you previously smoked daily, how long is it since you quit? *Number of years*

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you normally smoke per day? *Number of cigarettes*

How old were you when you began daily smoking? *Age in years*

How many years in all have you smoked daily? *Number of years*

E10. BODILY FUNCTIONS AND SAFETY

Would you feel safe by walking alone in the evening in the area where you live?

☐ Yes 1 2 3 ☐ A little unsafe ☐ Very unsafe

When it comes to mobility, sight and hearing, can you:
(Tick once for each line)

	Without problems	With some problems	With great problems	No
Take a 5 minute walk in fairly high pace?	☐	☐	☐	☐
Read ordinary text in newspaper, if necessary with glasses?	☐	☐	☐	☐
Hear what is said in a normal conversation?	☐ 1	☐ 2	☐ 3	☐ 4

Do you because of chronic health problems have difficulties with: *(Tick once for each line)*

	No difficulties	Some difficulties	Great difficulties
Move around in your home?	☐	☐	☐
Get out of your home by yourself?	☐	☐	☐
Participate in organization or other leisure time activities?	☐	☐	☐
Use public transport?	☐	☐	☐
Perform necessary daily shopping?	☐	☐	☐

E11. USE OF HEALTH SERVICES

How many times in the last 12 months have you been to/used:
(Tick once for each line)

	None	1-3 times	4 or more
A general practitioner (GP)	☐	☐	☐
Specialist *(private or out-patient clinic)*	☐	☐	☐
Emergency GP *(private or public)*.....	☐	☐	☐
Hospital admission	☐	☐	☐
Home nursing care	☐	☐	☐
Physiotherapist	☐	☐	☐
Chiropractor	☐	☐	☐
Municipal home care	☐	☐	☐
Dentist	☐	☐	☐
Alternative practitioner	☐	☐	☐

Are you confident that you will receive health care and home assistance if you need it?

YES ☐ 1 NO ☐ 2 Don't know ☐ 3

E12. FAMILY AND FRIENDS

Do you live: At home? ☐ 1 In an institution/shared apartment? ☐ 2

Do you live with:

	YES	NO
Spouse/ partner?.....	☐	☐
Other people?	☐	☐

How many good friends do you have?
Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include your children and other relatives.....

Number of friends ☐☐

How much interest do people show for what you do?
(Tick only once)

Great interest ☐ 1 Some interest ☐ 2 Little interest ☐ 3 No interest ☐ 4 Uncertain ☐ 5

How many associations, sport clubs, groups, religious communities, or similar do you take part in?
(write 0 if none)

Number ☐☐

E13. CHILDHOOD/YOUTH AND AFFILIATION

How long altogether have you lived in the county? ☐☐ years

How long altogether have you lived in the municipality? ☐☐ years

Where did you live most of the time before the age of 16?
(Tick one option and specify)

Same municipality..... ☐ 1

Another municipality in the county..... ☐ 2 Which one:_____

Another county in Norway ☐ 3 Which one:_____

Outside Norway ..... ☐ 4 Country: _____

Have you moved during the last five years?

No ☐ 1 Yes, once ☐ 2 Yes, more than once ☐ 3

E14. USE OF MEDICINES

With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here

Do you use?
(Tick once for each line)

	Now	previously, but not now	Never used
Blood pressure lowering drugs	☐	☐	☐
Cholesterol-lowering drugs	☐	☐	☐
Drugs for osteoporosis	☐	☐	☐
Insulin.....	☐	☐	☐
Tablets for diabetes	☐	☐	☐

How often have you during the last 4 weeks used the following medicines?
(Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week, but not daily	Daily
Painkillers non-prescription.....	☐	☐	☐	☐
Painkillers on prescription	☐	☐	☐	☐
Sleeping pills.....	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐
Other prescription medicines	☐	☐	☐	☐
	1	2	3	4

State the name of the medicines you are using now and the reason you are taking the medicines (disease or symptom):
(Tick for each duration you have used the medicine)

Name of the medicine: (one name per line):	Reason for use of the medicine:	How long have you used the medicine: Up to 1 year	How long have you used the medicine: One year or more
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

If there is not enough space here, you may continue on a separate sheet that you attach.

E15. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

How old were you when you started menstruating? *Age in years* ☐☐

How old were you when you stopped menstruating? *Age in years* ☐☐

How many children have you given birth to? *Number of children* ☐☐

Do you use, or have you ever used estrogen? *Total number of years*

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

If you use estrogen, which brand you use now?

_____

Have you ever used contraceptives pills? ..... Yes ☐ No ☐

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Appendix 3 c

2nd Questionnaire Tromsø 5

Visit 1, all

Label

Additional questions to the health survey in Troms and Finnmark 2001-2002

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The study 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 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 strictly confidential.

The information you give us may later be linked 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 unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed prepaid envelope. Thank you in advance for helping us.

Yours sincerely

Department of Community 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 ☐

Date of completion:

Day ☐☐ Month ☐☐ Year ☐☐☐☐

T1. NEIGHBORHOOD AND HOME

1.1 In which municipality did you live at the age of 1 year? *(If you have not lived in Norway, state country of residence instead of the municipality)*

_____

1.2 What type of house do you live in? *(Tick only once)*

- Detached house/villa ..... ☐ 1
- Farm ..... ☐ 2
- Flat/apartment ..... ☐ 3
- Terraced/semi-detached house ..... ☐ 4
- Institution/care home ..... ☐ 5
- Other ..... ☐ 6

1.3 How big is your house? ☐☐☐ *m² (gross)*

1.4 Are you bothered by: *(Tick once for each line)*

	No complaint	Little complaint	Severe complaint
Moisture, drought or coldness in your home	☐	☐	☐
Other forms of bad indoor climate	☐	☐	☐
Traffic noise (cars or aircraft)	☐	☐	☐
Other noise (industrial, construction, etc.)	☐	☐	☐
Neighbour noise	☐	☐	☐
Drinking water quality	☐	☐	☐
Air pollution from traffic	☐	☐	☐
Air pollution from wood/oil heating, factory etc.	☐	☐	☐

1.5 What home language did your grandparents have? *(Tick for one or more alternatives)*

	Norwegian	Sami	Kven/ Finnish	Other language
Mother's mother ...	☐	☐	☐	☐
Mother's father	☐	☐	☐	☐
Father's mother ...	☐	☐	☐	☐
Father's father	☐	☐	☐	☐

T1. NEIGHBORHOOD AND HOME (cont.)

1.6 What do you consider yourself as? *(Tick for one or more alternatives)*

Norwegian	Sami	Kven/ Finnish	Other
☐	☐	☐	☐

1.7 Do you feel that you have enough good friends? Yes ☐ No ☐

1.8 How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings or other associations? *(Tick only once)*

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

T2. PAID AND UNPAID WORK

2.1 If you have paid or unpaid work, how would you describe your work? *(Tick only once)*

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

2.2 Can you decide yourself how your work (paid or unpaid) should be organised? *(Tick only once)*

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

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

T3. TOBACCO

3.1 Do you smoke?

Yes, daily ☐ 1 Yes, sometimes ☐ 2 No, never ☐ 3

If "Yes, sometimes"

What do you smoke?

☐ Cigarettes ☐ Pipe ☐ Cigar/cigarillos

3.2 Have you used or do you use snuff daily?

Yes, now ☐ Yes, previously ☐ Never ☐

If YES:

How many years altogether have you used snuff? ☐☐ years

T4. ALCOHOL

4.1 Are you a teetotaller? ..... Yes ☐ No ☐

4.2 How many times a month do you normally drink alcohol? ..... ☐☐ *Number of times*

(Do not count low-alcohol beer. Put 0 if less than once a month)

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

Beer ☐☐ Wine ☐☐ Spirits ☐☐

(Do not count low-alcohol beer. Put 0 if you do not drink alcohol)

4.4 For approximately how many years has your alcohol consumption been at the same level you described above? ☐☐ years

4.5 Have you, in one or more periods in the last 5 years consumed so much alcohol that it has inhibited your work or social life?

Yes, at work ☐ 1 Yes, socially ☐ 2 Yes, both at work and social life ☐ 3 No, never ☐ 4

T5. FOOD AND DIETARY SUPPLEMENTS

5.1 Do you usually eat breakfast every day? ... Yes ☐ No ☐

5.2 How many times a week do you eat a warm dinner? ..... ☐ *times*

5.3 How important is it for you to have a healthy diet?

Very ☐ 1 Somewhat ☐ 2 Little ☐ 3 Not ☐ 4

5.4 Do you use the following dietary supplements?

	Yes, daily	sometimes	No
Iron tablets	☐	☐	☐
Calcium tablets or bonemeal	☐	☐	☐
Vitamin D supplements	☐	☐	☐
Cod liver oil	☐	☐	☐

T6. BODY WEIGHT

6.1 Do you currently try to change your body weight?

No ☐ 1 Yes, I try to gain weight ☐ 2 Yes, I try to lose weight ☐ 3

6.2 What weight would you be satisfied with (your "ideal weight")? ..... ☐☐☐ kg

T7. ILLNESSES AND INJURIES

7.1 Have you ever had:

Tick once for each question. Also give the age at the time. If you have had the condition several times, how old were you the last time

	Yes	No	Age last time
Severe injury requiring hospital admission	☐	☐	☐☐ years
Ankle fracture	☐	☐	☐☐ years
Peptic ulcer	☐	☐	☐☐ years
Peptic ulcer surgery	☐	☐	☐☐ years
Neck surgery	☐	☐	☐☐ years
Prostate surgery	☐	☐	☐☐ years

7.2 Do you have, or have you ever had:

(Tick once for each question)

	Yes	No
Cancer	☐	☐
Psoriasis.....	☐	☐
Thyroid disease	☐	☐
Glaucoma	☐	☐
Cataract	☐	☐
Osteoarthritis (arthrosis).....	☐	☐
Bent fingers	☐	☐
Skin contractions in your palms	☐	☐
Kidney stone	☐	☐
Appendectomy.....	☐	☐
Hernia surgery	☐	☐
Surgery/treatment for urine incontinence	☐	☐
Epilepsy.....	☐	☐
Poliomyelitis (polio)	☐	☐
Parkinson's disease.....	☐	☐
Migraine.....	☐	☐
Leg ulcer	☐	☐
Allergy and hypersensitivity:	Yes	No
Atopic eczema (e.g. childhood eczema)	☐	☐
Hand eczema.....	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy).....	☐	☐

7.3 Have you had common cold, influenza, gastroenteritis, etc. during the last 14 days? Yes ☐ No ☐

7.4 Have you during the last 3 weeks had common cold, influenza, bronchitis, pneumonia, sinusitis, or other respiratory infection? ..... Yes ☐ No ☐

7.5 Have you ever had bronchitis or pneumonia? ..... Yes ☐ No ☐

7.6 Have you during the last 2 years had bronchitis or pneumonia? *(Tick only once)*

No ☐ 1 1-2 times ☐ 2 More than 2 times ☐ 3

T8. SYMPTOMS

8.1 Have you in the last two weeks felt:
(Tick once for each question)

	No	A Little	A lot	Very much
Nervous or worried	☐	☐	☐	☐
Bothered by anxiety	☐	☐	☐	☐
Confident and calm	☐	☐	☐	☐
Irritable	☐	☐	☐	☐
Happy and optimistic	☐	☐	☐	☐
Down/depressed	☐	☐	☐	☐
Lonely	☐	☐	☐	☐
	1	2	3	4

8.2 Do you cough about daily for periods of the year? Yes ☐ No ☐

If YES:
Is your cough productive? ☐ ☐

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

8.3 Have you had episodes with wheezing in the chest? ☐ ☐

If YES:
Has this occurred: *(Tick once for each question)*

	Yes	No
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐

8.4 Do you get pain in the calf while walking Yes ☐ No ☐

If YES:
How long can you go before you notice the pain? ☐☐☐ *meter*

8.5 Do you get short-winded in the following situations?
(Tick once for each question)

	Yes	No
While walking fast on level ground or slight up hills	☐	☐
While walking calmly on level ground	☐	☐
While washing or dressing yourself	☐	☐
While resting	☐	☐

8.6 Do you have to stop because of short-windedness while walking in your own pace on level ground? Yes ☐ No ☐

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

If YES:
Has the complaint reduced your leisure time activity? Yes ☐ No ☐

For how long has the complaint endured in total?

approx. ☐☐ years and ☐☐ months

Has the complaint reduced your ability to work during the last year? *(Also applies to domestic workers and pensioners (Tick once)*

No/insignificantly	To some extend	Significantly reduced	Do not know
☐ 1	☐ 2	☐ 3	☐ 4

Have you been on sick leave due to these complaints during the last year? Yes ☐ No ☐ Do not work ☐

T8. SYMPTOMS (continue)

8.8 How often do you suffer from sleeplessness?
(Tick only once)

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

8.9 If you suffer from sleeplessness monthly or more frequently, what time of the year does it affect you most?

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

8.10 Have you in the last year suffered from sleeplessness to the extend that it has affected your ability to work ? Yes ☐ No ☐

8.11 Do you usually sleep during the day? ☐ ☐

8.12 How often do you suffer from urinary incontinence?

Never	☐ 1
Not more than once a month	☐ 2
Two or more times a month	☐ 3
Once a week or more	☐ 4

8.13 Are you able to walk down 10 steps without holding on to something (e.g. a handrail) Yes ☐ No ☐

8.14 Do you use glasses? ☐ ☐

8.15 Do you use a hearing aid? ☐ ☐

8.16 How is your memory?
(Tick once for each question)

	Yes	No
Do you forget what you just have heard or read?	☐	☐
Do you forget where you have placed things?	☐	☐
Is it more difficult to remember now than earlier?	☐	☐
Do you more often write memos now than earlier?	☐	☐

If "YES" on one of these questions; **Is this a problem in your daily life?** Yes ☐ No ☐

T9. MEDICINES

9.1 Do you use, or have you used any of the following medicines:

	Now	Previously, but not now	Age when used 1st time	Never used
Drugs for osteoporosis	☐	☐	☐☐ years	☐
Tablets for diabetes	☐	☐	☐☐ years	☐
Drugs for hypothyroidism (thyroxine)	☐	☐	☐☐ years	☐

9.2 Do you use any medicines which you take as injections? Yes ☐ No ☐

If YES:
Give the name of the medicines (for injection):
(one name per line)

_____

_____

T10. ILLNESS IN THE FAMILY

10.1 Tick for the relatives who have or have ever had any of the diseases: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Heart attack (heart wound)	☐	☐	☐	☐	☐	☐
Angina pectoris (heart cramp)	☐	☐	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐	☐	☐
Aneurysm.....	☐	☐	☐	☐	☐	☐
Gastric/duodenal ulcer	☐	☐	☐	☐	☐	☐
Hip fracture	☐	☐	☐	☐	☐	☐
Psychological problems ..	☐	☐	☐	☐	☐	☐
Allergy	☐	☐	☐	☐	☐	☐
Osteoarthritis (arthrosis) ..	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐

10.2 How many siblings and children do you have?

	Brothers	Sisters	Children
Number	☐☐	☐☐	☐☐

10.3 Do you usually do extra caring work because of illness etc. in your close family?

Yes, daily/almost daily ☐ 1 Yes, sometimes ☐ 2 No ☐ 3

10.4 Do you/your family receive home aid or home nursing care?..... Yes ☐ No ☐

	Yes	No	Age at death
10.5 Is your mother alive?	☐	☐	☐☐☐ years
10.6 Is your father alive?	☐	☐	☐☐☐ years

T11. MOBILE TELEPHONE

11.1 Do you have (own, rent, etc.) a mobile telephone?

Yes, always ☐ 1 Yes, sometimes ☐ 2 No ☐ 3

If Yes:

What do you use your mobile telephone for, and how often do you use it? *(Tick once for each line)*

	Number of times per day				
	30 or more	10-29	2-9	1 or less	Never
Conversations..	☐	☐	☐	☐	☐
Text messaging	☐	☐	☐	☐	☐
	12345				

T12. THE REST IS TO BE ANSWERED BY WOMEN ONLY

12.1 If you have given birth, fill in each child's birth year and how many months you breastfed after delivery.
(If you did not breastfeed, write 0)

Child:	Birth year:	Number of months breastfed:
1st child	☐☐☐☐	☐☐
2nd child	☐☐☐☐	☐☐
3rd child	☐☐☐☐	☐☐
4th child	☐☐☐☐	☐☐
5th child	☐☐☐☐	☐☐
6th child	☐☐☐☐	☐☐

(If more children, use additional sheet)

T12. THE REST IS TO BE ANSWERED BY WOMEN ONLY

12.2 If you still have menstrate or are pregnant:
What date did your last menstruation start?

Day ☐☐ Month ☐☐ Year ☐☐☐☐

12.3 If you no longer menstruate; why did your periods stop? *(Tick once)*

It stopped by itself ..... ☐ 1
Uterus surgery ..... ☐ 2
Surgically removed both ovaries ..... ☐ 3
Other reason (e.g. radiation, chemotherapy) ... ☐ 4

12.4 Do you use or have you used prescribed estrogen (tablets or patches)?..... Yes ☐ No ☐

If YES:
How old were you when you started taking estrogen ? ..... ☐☐ years

If you stopped using estrogen,
How old were you when you stopped taking estrogen?..... ☐☐ years

12.5 Do you use or have you used oral contraceptive pills?..... Yes ☐ No ☐

If YES:
How old were you when you started taking the pill?..... ☐☐ years

How many years in total have you taken the pills?.... *Number of years* ☐☐

If you have given birth:
How many years did you take the pill before your first delivery?... *Number of years* ☐☐

If you stopped taking the pill:
How old were you when you stopped?.... ☐☐ years

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

If YES:
How many times?..... ☐☐ times

12.7 How is your current menstruation status?

I have not had menstruation in the last year ☐ 1
I have regular menstruation ..... ☐ 2
I have irregular menstruation ..... ☐ 3

12.8 When you were 25-29 years old, how many days usually passed between the start of two periods?

Minimum ☐☐ days Maximum ☐☐ days Do not know ☐

The periods were of approximately equal length every time?..... Yes ☐ No ☐

How many days did a typical menstrual bleeding period last?... ☐☐ days

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

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