UNIVERSITY OF TROMSØ UIT

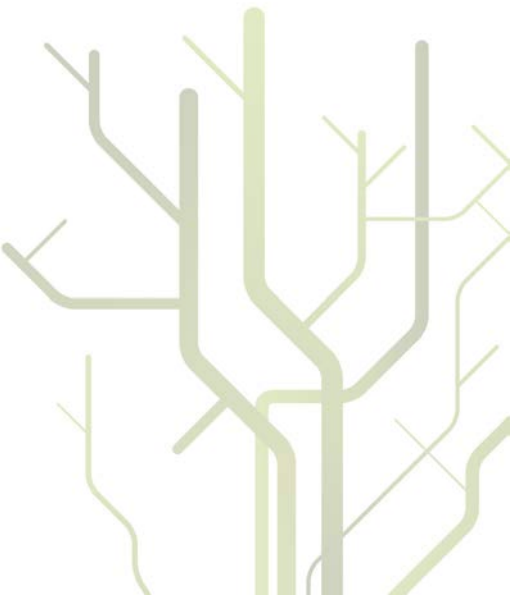
FACULTY OF HEALTH SCIENCES
DEPARTMENT OF COMMUNITY MEDICINE

Carotid atherosclerosis, vascular risk factors and relation to cognitive test results

The Tromsø Study 1994-2008

Kjell Arne Arntzen

A dissertation for the degree of Philosophiae Doctor
June 2012



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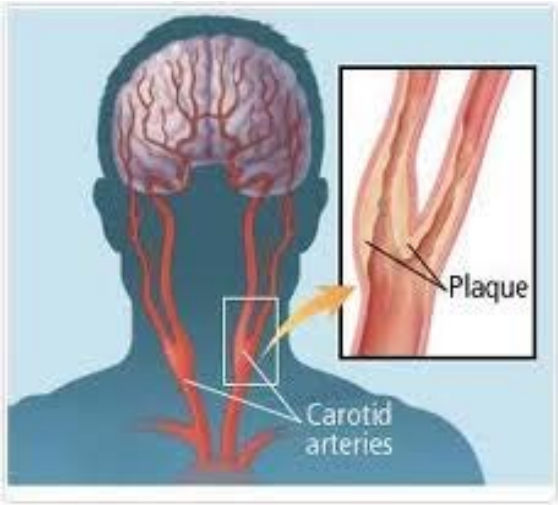

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The first preparations for this thesis began in 2006. Going from a busy clinical work as a neurologist to reading papers all day long was like jumping off a train at full speed. During these years I have learned a lot about epidemiology, statistics and scientific work, and I have very much learned to appreciate the valuable moments when I can be immersed in research without getting interrupted. I am very grateful for the opportunity I had to be a part of the Tromsø 6 study, going through the whole process from study planning and data collection to analyzing the data and writing papers. It is when you start to analyze your data you really understand what you did wrong in the planning phase and when collecting data. Many thanks to the University of Tromsø and the Department of Community Medicine who made conditions favorable for a (back then) young researcher who had his part time base there for over 5 years.

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Kjell Arne Arntzen

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Summary

The prevalence of dementia and cognitive impairment is rising worldwide as the number of elderly people increases in most countries. Vascular risk factors and carotid artery atherosclerosis have in some epidemiological studies been associated with increased risk of cognitive decline. The carotid artery is essential for blood supply to the brain, but is also vulnerable to atherosclerosis. The degree of atherosclerosis in the carotid artery can easily be measured by ultrasonography.

The population-based Tromsø study, with repeated screening surveys of the Tromsø population, has made it possible to follow participants prospectively. Repeated carotid ultrasound scanning and cognitive test assessments have provided a unique opportunity for assessing change in atherosclerosis and change in cognitive test scores. In this study we assessed the impact of different vascular risk factors on scores in three cognitive tests after 7 years of follow-up, and studied if carotid atherosclerosis and progression of atherosclerosis were independent risk factors for lower cognitive test scores and cognitive decline in a middle–aged stroke-free population.

We found that diabetes, smoking and systolic blood pressure were consistent and independent risk factors for lower cognitive test results after 7 years follow-up in both genders. Physical inactivity was associated with lower scores in women. Carotid atherosclerosis measured as total plaque area and number of plaques predicted lower scores on the verbal memory test 7 years later, whereas the average of plaque scores, measured at baseline and at follow-up, was associated with lower scores on all the cognitive tests in this study. Progression of carotid plaques over 7 years was associated with lower scores on the digit symbol coding test and the tapping test. We found no association between plaque scores and cognitive decline from 7 to 13 years of follow-up.

Sammendrag

Forekomsten av kognitiv svekkelse og demens øker i takt med at det blir stadig flere eldre i samfunnet. Vaskulære risikofaktorer og aterosklerose i carotisarteriene (halspulsårene) har i noen befolkningsstudier vært assosiert med økt risiko for kognitiv svekkelse. Carotisarteriene forsyner store deler av hjernen med blod, men er samtidig utsatt for aterosklerose. Graden av ateroslerose i carotisarteriene kan måles med ultralyd.

Tromsøundersøkelsen er en befolkningsundersøkelse med gjentatte screeningundersøkelser som har gjort det mulig å følge deltakerne over mange år. Repeterte ultralydundersøkelser og testing av kognitiv funksjon har gitt oss en unik mulighet til å måle endring i aterosklerose og kognitive testskår over tid i de samme deltakerne. Målet med denne studien var å se på ulike vaskulære risikofaktorers betydning for hvordan deltakerne skåret på tre kognitive tester 7 år senere, og å avgjøre om aterosklerose og progresjon av aterosklerose i carotisarteriene var uavhengige risikofaktorer for lavere skår på de kognitive testene og for fall i testskår fra 7-13 års oppfølging hos personer som ikke har hatt hjerneslag.

Vi fant at diabetes, røyking og høyt blodtrykk var assosiert med dårligere kognitive testskår etter 7 års oppfølging. Fysisk inaktivitet var assosiert med lavere skår hos kvinner. Aterosklerose i carotisarteriene, målt som totalt plakkareal eller antall plakk predikerte lavere skår på den verbale hukommelsestesten etter 7 år, mens gjennomsnittlig plakkskår mellom start og 7 års oppfølging var assosiert med lavere skår på alle de kognitive testene. Progresjon av aterosklerose over 7 år var assosiert med lavere skår på tall-symbol koding test og på tappetesten. Vi fant ingen assosiasjon mellom aterosklerosemålene og fall i kognitiv funksjon fra 7 til 13 års oppfølging.

List of papers

I. Arntzen KA, Schirmer H, Wilsgaard T, Mathiesen EB. **Impact of cardiovascular risk factors on cognitive function. The Tromsø Study.** Eur J Neurol. 2011;18(5):737-43.

II. Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. **Carotid atherosclerosis predicts lower cognitive test results: A 7 years follow-up study in 4371 stroke-free subjects. The Tromsø Study.** Cerebrovasc Dis. 2012;33(2):159-165.

III. Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. **Carotid artery plaque progression and cognitive decline. The Tromsø Study 1994-2008.** Eur J Neurol. 2012 Apr 27. [Epub ahead of print]

Abbreviations

AD: Alzheimer's disease

APOE: Apolipoprotein E

Bulb: Bulbus caroticus

BMI: Body mass index

CCA: Common carotid artery

CI: Confidence interval

FW: Far wall

HDL: High density lipoprotein

ICA: Internal carotid artery

IMT: Intima-media thickness

MCI: Mild cognitive impairment

MMSE: Mini-Mental State Examination

MRI: Magnetic resonance imaging

NW: Near wall

OR: Odds ratio

SD: Standard deviation

VaD: Vascular dementia

WML: White matter lesions

1. Introduction

1.1 Epidemiology of dementia and cognitive impairment

Cognitive impairment and dementia are major health problems worldwide. By linear extrapolation of estimates from 2005, about 35 million people suffer from dementia worldwide, and the prevalence is expected to double every 20 years provided that no effective preventive strategy becomes available and no change in mortality (1). Forty-three percent of dementia cases will be in need of a high level of health care equivalent to that of a nursing home (2). The prevalence of dementia and cognitive impairment increases by age, and in a study based on 11 European cohorts on persons above 65 years of age, the age-standardized prevalence of dementia (all causes) was found to be 6.4 %, increasing from 0.8% in the group 65-69 years to 28.5% at age 90 years and older. The frequency nearly doubles every 5 years of age over 65 years (3). Some studies on American populations found even higher prevalence estimates (4, 5), but the prevalence seems to be similar in most Western societies (Figure 1).

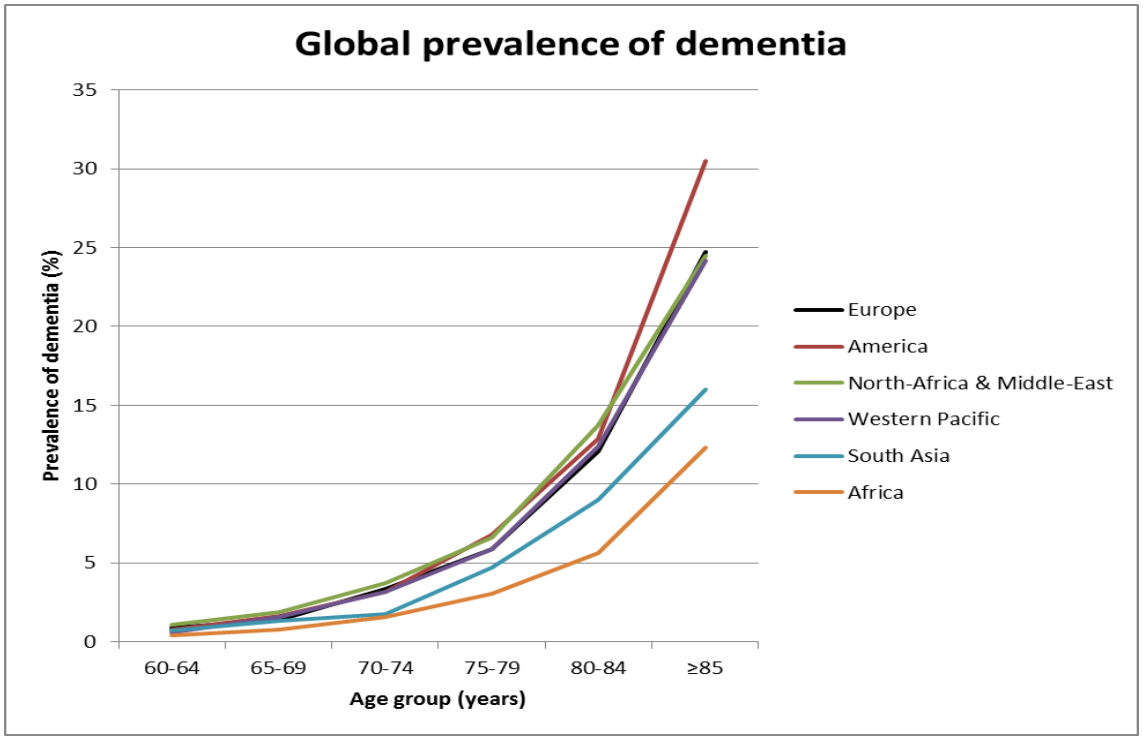


Figure 1. Global prevalence of dementia by age-groups. Based on data from Ferri et. Al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366:211-17 (1)

If cases of mild cognitive impairment (MCI) are taken into account, the total prevalence of cognitive impairment will probably be the double of what is estimated of dementia alone, depending on how MCI is defined (6-8). Because of increased life expectancy due to better health care and living conditions, and large birth rates in the years after World War II, a demographic shift towards a higher proportion of elderly is expected in the next decades in most Western countries. In Norway the proportion of elderly over 67 years of age is expected to double in the next 30-40 years (Figure 2). Unless better prevention strategies or treatment options become available, this will lead to a substantial increase in the prevalence of cognitive impairment and dementia.

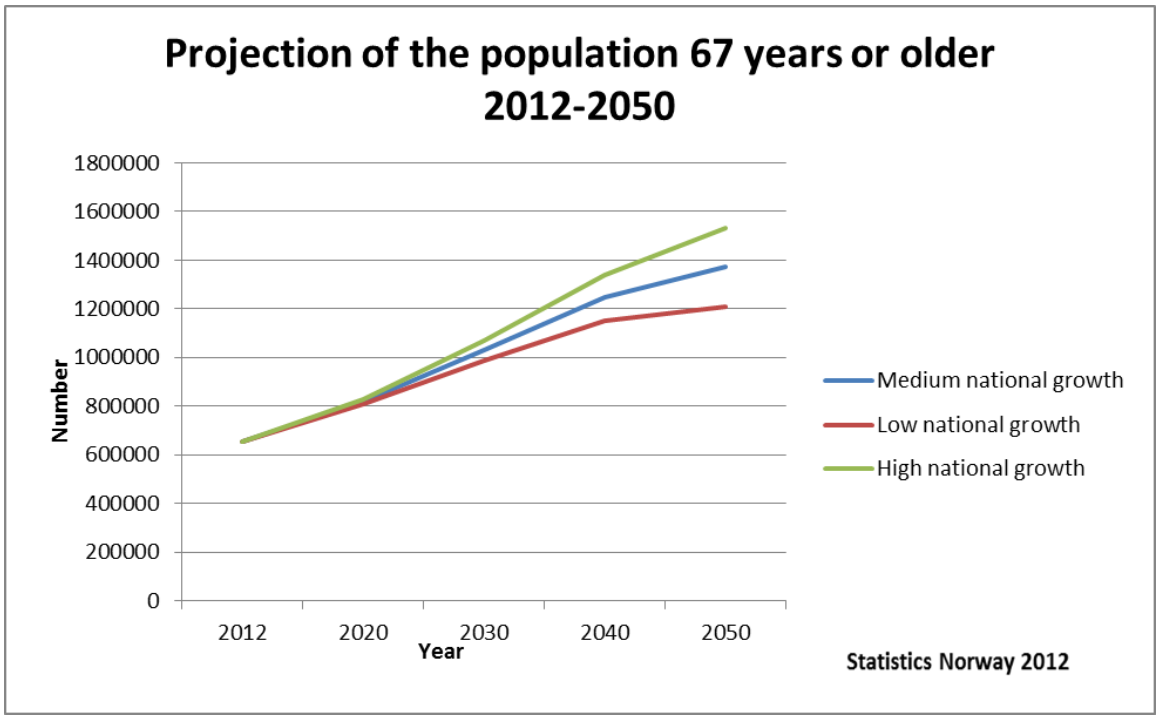


Figure 2. Population projection of the number of people 67 years or older in Norway from 2012 to 2050. Based on estimates from Statistics Norway (Statistisk sentralbyrå).

Alzheimer's disease (AD) is the major subtype of dementia, accounting for 65-70% of all cases, followed by vascular dementia (VaD) with 15-25% (3, 5). Alzheimer's disease progresses slowly over several years from normal cognitive function through MCI to

dementia, which gives a window for possible preventive efforts (6). Vascular dementia is caused by cerebral vascular lesions, and may occur acutely as a result of a strategic stroke or progressively due to several consecutive minor strokes or hypoperfusion to the brain. Identification and modification of risk factors in order to avoid or to delay the development of the two major types of dementia, may have great impact on public health. For example a 5 year delay in the onset of AD could reduce the prevalence of AD by 50%. The estimated worldwide prevalence of AD alone is predicted to reach more than 100 million people in 2050, which means that 1 in 85 persons worldwide will have AD. If interventions could delay both disease onset and progression by only 1 year, there would be nearly 9.2 million fewer cases of AD worldwide in 2050, with nearly the entire decline attributable to decrease in persons needing a high level of health care (2).

No current treatment can restore already non-functioning and lost neurons in demented patients, and treatment aimed at reversion of an existing brain damage is not likely to appear in the nearly coming years. To decrease the burden of dementia, the focus should therefore be on either primary prevention or secondary prevention to stop the progression of dementia in early stages. Primary and secondary prevention of VaD is in some degree possible by reduction of vascular risk factor levels and prevention of vascular disease. Currently, only symptomatic treatment is available for AD (cholinesterase inhibitors and the NMDA-receptor antagonist memantine). Disease-modifying drug have been tested, but results have so far been disappointing (9, 10). An effective primary prevention strategy would be the most preferable both to patient and society, but has so far not been established. Revealing possible treatable risk factors for cognitive impairment and dementia would be the first step toward a preventive strategy to lower the burden of cognitive impairment and dementia in society. Risk factors for prevalent diseases and symptoms can be assessed in cohort studies. Exploring risk factors for cognitive impairment in general populations could give valuable information on which factors that possibly could have the greatest impact on prevention of cognitive impairment.

1.2 Vascular risk factors and relation to cognitive impairment and dementia

Dementia caused by vascular changes was in the early days of modern medicine referred to as senile dementia due to hardening of arteries, but was replaced by the term multi-infarct dementia that was introduced in the late 1960s (11). The concept of vascular dementia gained ground in the early 1990s in order to refine the description of dementias caused by cerebral vascular changes. Vascular dementia was defined as dementias caused by multi-infarcts, strategic single infarcts, hemorrhages, cerebral small vessel disease, or hypoperfusion of the brain, with several subgroups (12, 13). However, the magnitude of vascular changes needed to cause dementia has been difficult to define, and this together with different clinical and research criteria in use, have given rise to a debate about the concept of vascular dementia (14). In recent years, the term vascular cognitive impairment is used to cover the whole scale from mild cognitive impairment to dementia caused by vascular changes, as well as cases of mixed dementias of vascular and degenerative causes (15). Risk factors for vascular cognitive impairment are thought to be the same as for stroke and include the traditional vascular risk factors; hypertension, smoking, high total-cholesterol, diabetes, physical inactivity and heavy alcohol consumption in addition to atherosclerosis, atrial fibrillation, heart failure, high age and low socioeconomic status (11, 15, 16).

In the first years after Alois Alzheimer described the disease of his famous patient Auguste D. in 1906, AD was thought to be a rare degenerative pre-senile dementia, while senile dementia caused by cerebral arteriosclerosis was perceived as the dominating cause of dementia. The pathological hallmarks of AD were amyloid plaques and intraneuronal tangles. Although some early investigators believed that also AD could be caused by cerebral arteriosclerosis, pathological studies in the mid- 20th century found an inconsistent relationship between AD and cerebral atherosclerosis, and AD was classified as a pure degenerative disease (17). In the beginning of the 1990s, pathological studies found that apolipoprotein E (APO E), involved in cholesterol

transport, was a constituent of amyloid plaques in Alzheimer's disease patients (18, 19). An association between the epsilon 4 (ε4) genotype of APO E and increased risk of AD was found in epidemiological studies, and led to a new interest in vascular changes in AD (20). During the last twenty years epidemiological studies have found associations between the vascular risk factors smoking, hypertension, high total-cholesterol, diabetes, physical inactivity, obesity and AD (21-24). Also, pathological studies have found that cerebral vascular changes is not unusual in AD, leading to the concept of mixed dementia of VaD and AD (25). Some authors have proposed that the neurodegenerative process of late-onset sporadic Alzheimer's disease may be triggered by vascular changes (26). If this is true, vascular risk factors and atherosclerosis could contribute to 80-90% of all cases of dementia.

1.3 Carotid atherosclerosis and relation to cognitive impairment and dementia

Atherosclerosis is a pathological process of the arterial wall, which in advanced stages cause vessel narrowing and occlusion. The traditional risk factors for cardiovascular disease and stroke, such as hypertension, smoking, total cholesterol and diabetes are also risk factors for progression of atherosclerosis (27, 28). The carotid arteries are vulnerable to atherosclerosis, and because they supply blood to the brain, vessel narrowing and embolisms from carotid atherosclerosis could cause stroke and subsequent cognitive impairment (29, 30). Some studies also found that carotid atherosclerosis was independently associated with poorer cognitive function in subjects without a clinical stroke (31, 32).

Ultrasound is an easily assessable and non-invasive method to measure the different stages of the atherosclerotic process in the carotid artery. The arterial wall consists of three layers, the intima, the media and the adventitia. Atherosclerosis is mainly an intimal process with deposition of cholesterol, inflammation and cell infiltration. Ultrasound cannot distinguish between the intima- and media-layer, but the intima-media thickness (IMT) of the arterial vessel wall can be assessed (29). Atherosclerotic

plaques usually occur at sites of non-laminar turbulent flow such as the carotid bifurcation and the proximal internal carotid artery (ICA), and measurement of thickening in the arterial intima-media layer in these areas are likely to represent early stages in the atherosclerotic process. However, a diffuse thickening of the carotid artery intima-media layer can also represent a hypertensive hypertrofic response of the smooth muscle cells of the medial-layer related to changes in local shear stress and tensile stress to the vessel wall. In clinical and epidemiological studies IMT has usually been measured in the near and the far wall of the distal part of the common carotid artery (CCA-IMT), the carotid bifurcation (Bulb-IMT) and the proximal internal carotid artery (ICA-IMT).

Atherosclerotic plaques are localized manifestations of atherosclerosis. Criteria for ultrasound definition of an atherosclerotic plaque have varied in different studies (33). A visually localized protrusion of the vessel wall of more than 50% of the adjacent (normal) IMT is a widely used definition of a plaque and is also used in the Tromsø study (34). Plaque occurrences, number of plaques, plaque thickness, plaque area, plaque volume and plaque echogenicity are different measures that can be used to assess the amount and burden of carotid atherosclerosis. Small plaques do not significantly affect the blood flow or blood velocity, but increasing plaque size or number leads to narrowing of the vessel lumen, stenosis and increased risk of embolization and hypoperfusion. Compared to early intima-media thickening, formed plaques represent more advanced atherosclerosis. Studies have indicated that total plaque burden measured as total plaque area, the sum of all plaque areas in the distal CCA, bifurcation and proximal ICA, may be a sensitive tool for prediction of clinical cardiovascular disease (35). Previous studies have found that total plaque area predicts future stroke and myocardial infarction (36, 37). In the Tromsø Study, total plaque area was a stronger predictor of stroke and myocardial infarction than was IMT (38, 39).

Previous population-based studies on the relation of carotid atherosclerosis and cognitive function have assessed the impact of a one-time measure of atherosclerosis. Most of the studies have focused on the impact of carotid IMT and stenosis and not carotid plaques, and no population-based studies have assessed the progression of carotid plaques in relation to cognitive function (40). In some studies, cognitive impairment and decline were independently predicted by both carotid IMT (32, 41, 42) and carotid stenosis (31, 32, 43), but results are conflicting as some studies in middle-aged populations did not observe the same relationship (23, 44). In two studies, carotid IMT, but not carotid stenosis or atherosclerotic plaques, was associated with increased risk of AD (45, 46). Little is known about how carotid atherosclerosis in middle age affects cognitive test scores, as most studies are done in the elderly (>65 years). Measurements of progression of carotid atherosclerosis over years could bring stronger evidence of a causative association between carotid atherosclerosis and cognitive impairment.

2. Aims of the thesis

The general objective of this thesis was to study possible preventable risk factors for cognitive impairment in the general population.

The specific aims were:

- To assess and compare the impact of traditional cardiovascular risk factors on cognitive test scores after 7 years of follow-up in a stroke-free middle-aged general population.

-To study if ultrasound-assessed carotid atherosclerosis measured as IMT, the number of plaques and total plaque area is associated with lower cognitive test results in a stroke-free middle-aged general population after 7 years of follow-up.

-To explore if progression of carotid atherosclerosis from baseline to 7 years follow-up is associated with lower cognitive test scores at 7 years follow-up and with cognitive decline from 7 to 13 years follow-up.

3. Subjects and methods

3.1 Study population-The Tromsø study

Subjects were participants in The Tromsø Study, a longitudinal population-based study in the municipality of Tromsø, Norway (47). A total of six cross-sectional screening surveys (Tromsø 1-6) with 6-7 years interval have so far been carried out from 1974 until 2008. Cardiovascular disease was initially the main focus of the study, but other research areas have been added throughout the years. Ultrasound examination of the right carotid arteries was done the first time in Tromsø 4 in 1994/1995, and repeated in Tromsø 5 in 2001/2002 and in Tromsø 6 in 2007/2008. Cognitive testing was done in Tromsø 5 and 6. The Tromsø population is mainly Caucasian. In 1994/1995, less than 2% of the population was immigrants of non-Western origin. All subjects who participated in Tromsø 4-6 were asked to give written consent to medical research. They are free to withdraw their consent at any time, and also to give new consent later on, for example when participating in a new survey. Thus, the number of participants with valid written medical consent may vary over time.

Tromsø 4 comprised two screening visits 4-12 weeks apart. To the first visit, all citizens aged 25 and above were invited, and 27158 attended (77% attendance rate). All participants who were between 55-74 years old and 5-10% samples of the remaining 5-year birth cohorts aged 25-85 years were invited to a more comprehensive second visit examination, and the 7965 subjects who attended (76% of the eligible) constituted the baseline for this study (Figure 3). Vascular risk factors were assessed in in the 1st visit in Tromsø 4, and carotid ultrasound examination was performed in 6727 subjects who attended the 2nd visit (1238 subjects not scanned for logistic reasons). All subjects who attended both visits of Tromsø 4 and who were still registered as inhabitants of Tromsø (n=6969) were invited to the 2nd visit in Tromsø 5, and 5939 subjects attended (85%)[1]. A total of 5493 subjects attended cognitive testing in Tromsø 5 (446 subjects not tested because of logistic reasons). Of those who underwent carotid ultrasound examination in

[1] Not 6982 (invited) and 5898 (attended) as stated in Paper I and II.

Tromsø 4, 4858 subjects were rescanned in Tromsø 5. All individuals who had taken part in the 2nd visit of Tromsø 4 as well as individuals who were aged 50-62 or 75-84 and a 20 % random sample of subjects aged 63-74 were invited to the 2nd visit of Tromsø 6, and 7307 attended. Of those eligible who also attended Tromsø 4, the attendance rate was 74 %. A total of 2737 subjects attended cognitive testing in both Tromsø 5 and 6.

In *Paper I* we investigated to role of cardiovascular risk factors assessed in Tromsø 4 in relation to cognitive test scores in stroke-free individuals after 7 years follow-up in Tromsø 5. Of the 5493 subjects who attended both visits of Tromsø 4 and cognitive testing in Tromsø 5, 51[2] did not have a valid written consent to medical research when the dataset was generated in 2007 and were excluded from analyses, leaving 5442 subjects with valid data on cognitive testing. We excluded 101 subjects with self-reported stroke prior to participation in the cognitive testing in Tromsø 5, and 308 subjects who did not have complete baseline data on the cardiovascular risk factors used in the analyses, leaving 5033 subjects who were included in Paper I.

In *Paper II* we investigated the association between ultrasound-assessed carotid atherosclerosis in Tromsø 4 and cognitive testing in Tromsø 5. Of the 5493 who attended both visits in Tromsø 4 and attended cognitive testing in Tromsø 5, 31 was excluded for not having a valid written consent to medical research when the dataset was generated in 2011. Participants of the Tromsø study are being followed-up with registration of incident stroke and other cardiovascular diseases. Strokes are identified through linkage to diagnosis registry at the University Hospital of North Norway (UNN) and the national Cause of Death Registry, and adjudication of hospitalized and out-of hospital first-ever strokes is performed by an independent endpoint committee based on data from hospital and out-of hospital journals (48). Based on these data, 192 subjects were excluded due to previous validated stroke prior to cognitive testing, 635

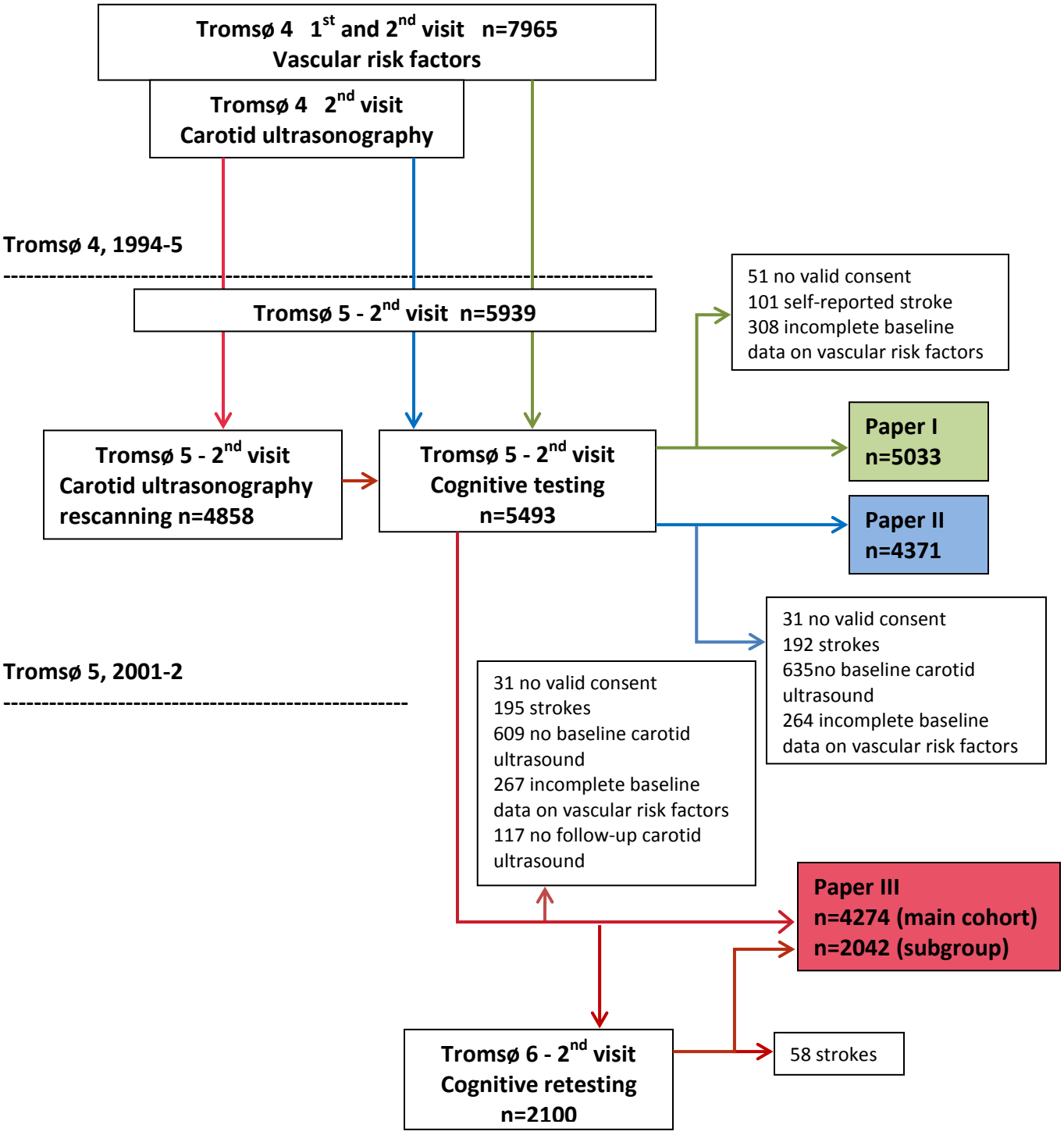
[2] Not 54, as stated in Paper I. The number 54 referred to the 51 and additional 3 more subjects without consent who participated in the 2nd visit of Tromsø 5, but not in cognitive testing.

due to lack of carotid ultrasound data at baseline, and 264 due to incomplete data on cardiovascular risk factors, leaving 4371 in the cohort of Paper II.

In *Paper III* we studied the association between the progression of carotid atherosclerosis from Tromsø 4 to 5 and cognitive test scores in Tromsø 5 and cognitive decline from Tromsø 5 to 6. Of the 5493 who attended both visits of Tromsø 4 and cognitive testing in Tromsø 5, 31 was excluded for not having a valid written consent to medical research (in 2011), 195 were excluded due to validated stroke prior to cognitive testing in Tromsø 5. Three more strokes than in Paper II were identified in a new update of the stroke registry that took place in the period between Paper II and III. Baseline carotid ultrasound data were lacking in 609 subjects and 267 subjects had incomplete baseline data of cardiovascular risk factors and were excluded. Follow-up carotid ultrasound data were lacking in 117 individuals, leaving 4274 subjects who were included in the study. Of these subjects, 2100 were re-tested with at least one of the three cognitive tests in Tromsø 6. Subjects with a validated diagnosis of stroke in the follow-up period from Tromsø 5 to 6 (n=58) were excluded from analyses, leaving a subgroup of 2042 subjects who were included in the second part of the study.

Information about the study population and the number of subjects in each paper is summed up in a flow chart (Figure 3). The studies were approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health. All participants have given written consent to medical research.

Figure 3. Flowchart of the study population



3.2 Cardiovascular risk factors

At baseline in Tromsø 4, two self-administrated questionnaires were filled in, non-fasting blood samples were taken, and standardized measurement of weight, height, and blood pressure were performed. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor, Tampa, FL, USA) by specially trained personnel. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Non-fasting serum cholesterol and triglycerides were analyzed by standard enzymatic methods. Analyzes were performed at the Department of Clinical Chemistry, University Hospital of North-Norway. Information on education, smoking habits, physical activity, depression, diabetes, stroke and coronary heart disease were obtained from self-administered questionnaires (Appendix A). Education was assessed in four categories, primary/part secondary school (7-10 years), secondary/O-level (11-12 years), high school/A-level and college/university less than 4 years (12-15 years) and college/university 4 years or more (>15 years). Smoking was defined as daily smoking of sigarettes, cigars or smoking a pipe. Physical activity was assessed by two questions on how many hours of light and hard physical activity the participants performed per week. Light activity was defined as not sweating or out of breath and hard physical activity was defined as sweating/out of breath. Answers were dichotomized to physically active and inactive groups, where physically active was defined as exercise with sweating/out of breath $\geq$ 1 hour per week, or $\geq$ 3 hours per week of light activity without sweating/out of breath. Diabetes was defined as self-reported diabetes and/or regular use of insulin or oral antidiabetics. Coronary heart disease was defined as previous myocardial infarction and/or prevalent angina. Depression was assessed by the question 'Have you in the last two weeks felt down/depressed?', where answers in the two upper of four categories (no, a little, a lot, or very much) were defined as depression. Use of medication was obtained from self-administered questionnaires (Appendices A-D).

3.3 Carotid ultrasound examination

B-mode ultrasonography was performed with an Acuson Xp10 128, ART-upgraded duplex scanner equipped with a 7.5 MHz linear array transducer. Different sonographers did the baseline and follow-up scanning, and to ensure equal and standardized examination techniques and measurement procedures, all sonographers completed a 2-month pre-study training protocol following the guidelines in Appendix E. Details about the ultrasound methods and reproducibility have been published previously (34, 49, 50). Due to logistic reasons, only the right carotid artery was scanned. The far- and near walls of the right CCA, bulb and ICA were scanned for plaque presence. A plaque was defined as a localized protrusion into the vessel lumen with thickening of the vessel wall of more than 50% compared to the adjacent IMT (Figure 4).

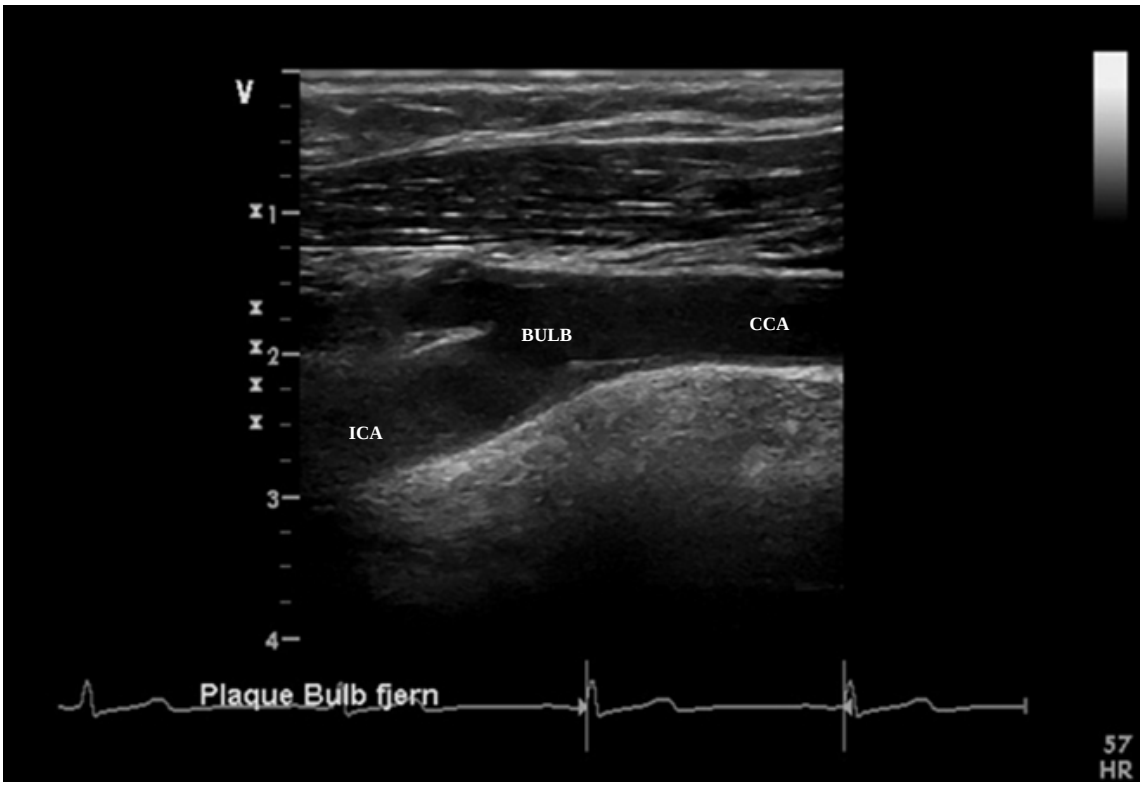


Figure 4. The carotid bifurcation with an atherosclerotic plaque in a typical location in the far wall of the bulb. The adjacent IMT is visible on both sides of the plaque.

Total plaque area was calculated as the sum of all plaque areas (34). Standardized automated measurement of R-wave triggered IMT was performed in 10mm segments of

the CCA far wall (CCA-FW-IMT) and near wall (CCA-NW-IMT) and the far wall of the bulb (BULB-FW-IMT) (33), and mean IMT from 3 pre-selected images was calculated for each location and referred to as the mean total IMT. If present in the predefined location of interest, plaques were included in the IMT measurements. Final reading of both IMT and plaque data was done off line by the researchers. Measurements of IMT were analysed off line by a semi-automated computerized edge-detection program (51).

3.4 Cognitive testing

Three cognitive tests were chosen by a group of neuropsychologists and epidemiologists for use in Tromsø 5. All tests were chosen because of their ability to detect early cognitive decline and their feasibility as screening tests in an epidemiological setting with a large number of participants. The tests had previously been found to predict cognitive decline in other population-based studies (42, 52).

The twelve word memory test is a test of short time verbal memory with immediate free recall of 12 nouns shown written on a board and also pronounced one at a time with a 5-second interval (52). The participants then had 2 min to recall the words, and one point was given for each word correctly recalled.

Digit-Symbol Coding test, a part of the Wechsler Adult Intelligence Scale (WAIS) is used to examine psychomotor speed, attention and mental flexibility (53). The digit-symbol substitution task consists of rows containing small blank squares, each paired with a randomly assigned number from one to nine and with a printed key above that pair each number with a different nonsense symbol (Appendix F). Subjects were asked to consecutively fill in as many as possible of the blank spaces with the corresponding symbol as quickly and accurately as possibly over 90 seconds.

Tapping test is a test mainly of psychomotor tempo. The subjects were instructed to tap as many times as possibly in 10 seconds with their index finger on a computer which

registered the number of taps. The task was repeated four times with both dominant hand and non-dominant hand (54). The mean of the average score of the three last trials on each hand was used in the analyses.

3.5 Statistical methods

The SAS statistical software package (SAS®, V9.2, SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Baseline characteristics were presented as means (standard deviation) or numbers (percent) in the three papers. In paper I, the association between vascular risk factors and cognitive test results were assessed in a multivariable linear regression model adjusted for age, education, systolic blood pressure, total-cholesterol, HDL-cholesterol, body mass index, current smoking, physical activity, diabetes, coronary heart disease and self-reported depression, and presented separately for men and women. All continuous variables were dichotomized to fit a logistic regression model to measure the risk of scoring in the lowest quintile on each cognitive test. Descriptive statistics on scores and change in scores on cognitive tests and carotid atherosclerosis were presented in paper II and III. The relation between different measures of carotid atherosclerosis scores and cognitive test results were assessed in univariable and multivariable regression models adjusted for sex, age, education, depression and vascular risk factors. Standardized regression coefficients were used as effect size to compare results between the independent variables (paper I), and also between each cognitive test (paper II and III). The model assumptions were confirmed by graphical inspection of residuals. Possible two-way interactions were assessed by adding to the models cross product terms between each of the exposure variables and each of the adjustment variables. Multicollinearity between the independent variables was low, with a variance inflation factor < 1.6 for all variables in all the three papers. Details of the statistical methods are described in detail in Paper I-III.

4. Results

Paper I - Impact of cardiovascular risk factors on cognitive function. The Tromsø Study.

In this study we assessed the impact of different cardiovascular risk factors on cognitive test results in a stroke-free middle-aged general population (mean age 58.2 years in women and 58.8 years in men). Performance on the three cognitive tests is shown by sex, age and education level in table 1 (same as Webtable 1, Paper 1). Increasing age and lower education level were consistently associated with lower cognitive performance on all three tests.

In the multivariable linear regression analyses adjusted for age, education level, depression and vascular risk factors, smoking showed the most consistent inverse association with cognitive test results on all tests in both men and women. Physical activity was associated with better performance on the verbal memory test and the coding test in women, but no association was seen in men. Systolic blood pressure was inversely associated with cognitive performance on the coding and the tapping test in women, and on the verbal memory test in men. Diabetes was significantly associated with lower scores on the tapping test and the coding test in women, and on the verbal memory test and the coding test in men. We found no significant associations between total-cholesterol, HDL-cholesterol or coronary heart disease and any of the cognitive tests. BMI was negatively associated with performance on the coding test in men.

In the logistic regression models, diabetes showed the strongest estimates for lower test scores. The odds ratio (OR) of a score in the lowest quintile on the verbal memory test in men was 2.98 (95% CI 1.56-5.68), and 2.33 (95 % CI 1.25-4.35) on the coding test and on the tapping test 2.55 (95% CI 1.43-4.55) in women.

Table 1. Performance on cognitive tests by sex, age and education level. Tromsø 5.

	Education	Age years					
		25-49y (n)	50-54y (n)	55-59y (n)	60-64y (n)	65-69y (n)	>70y (n)
Verbal memory test	Scores are given as the number of right words recalled						
Men	Primary school	6.93 (89)	5.98 (58)	5.86 (207)	5.27 (226)	5.05 (166)	4.64 (109)
	Secondary school	7.25 (95)	6.71 (49)	6.37 (158)	5.82 (132)	5.45 (85)	5.17 (72)
	High school/College<4y	7.85 (73)	6.93 (43)	6.59 (94)	6.58 (72)	6.30 (57)	5.41 (27)
	College/university ≥4y	8.31 (36)	8.33 (18)	8.00 (62)	6.82 (22)	6.18 (22)	6.50 (12)
Women	Primary school	7.40 (60)	6.64 (235)	6.17 (341)	5.99 (291)	5.58 (307)	4.85 (217)
	Secondary school	7.91 (99)	7.02 (118)	7.17 (141)	6.52 (92)	6.12 (102)	5.79 (34)
	High school/College<4y	8.10 (89)	7.82 (72)	7.64 (59)	7.07 (45)	6.97 (34)	5.65 (17)
	College/university ≥4y	9.12 (47)	8.31 (42)	7.36 (53)	6.93 (28)	7.00 (10)	6.71 (7)
Coding test	Scores are given as the number of right symbols coded						
Men	Primary school	34.83 (89)	31.05 (59)	27.42 (219)	21.94 (235)	19.48 (182)	16.53 (118)
	Secondary school	42.48 (97)	36.54 (46)	31.95 (155)	27.27 (132)	25.34 (90)	20.88 (72)
	High school/College<4y	49.85 (72)	39.84 (45)	38.02 (98)	33.34 (71)	28.30 (60)	26.68 (28)
	College/university ≥4y	48.71 (38)	47.72 (18)	42.85 (65)	39.14 (22)	35.22 (22)	30.83 (12)
Women	Primary school	44.19 (63)	33.43 (237)	29.04 (349)	24.46 (300)	21.65 (310)	17.05 (232)
	Secondary school	48.05 (95)	40.51 (122)	35.32 (151)	31.08 (93)	28.58 (106)	25.83 (36)
	High school/College<4y	52.04 (93)	48.21 (72)	38.97 (62)	32.60 (48)	33.53 (34)	27.29 (17)
	College/university ≥4y	55.36 (47)	47.05 (41)	40.75 (53)	37.14 (29)	38.11 (9)	33.14 (7)
Tapping test dominant hand	Scores are given as the average number of taps in 10 seconds						
Men	Primary school	61.56 (98)	57.45 (58)	56.29 (234)	53.13 (243)	51.22 (186)	47.99 (128)
	Secondary school	62.57 (106)	59.20 (46)	58.27 (171)	56.29 (139)	52.87 (92)	51.78 (76)
	High school/College<4y	62.40 (72)	62.20 (45)	61.26 (100)	57.58 (74)	55.40 (56)	51.54 (29)
	College/university ≥4y	64.57 (36)	61.96 20)	62.66 (71)	58.75 (24)	56.61 (24)	51.78 (13)
Women	Primary school	54.52 (63)	51.80 (249)	51.06 (376)	48.63 (313)	46.31 (318)	41.01 (236)
	Secondary school	58.75 (96)	54.80 (125)	54.74 (158)	52.47 (98)	49.78 (107)	44.51 (36)
	High school/College<4y	60.78 (97)	58.25 (71)	56.85 (65)	53.28 (50)	52.58 (38)	47.66 (18)
	College/university ≥4y	59.68 (49)	58.13 (42)	55.93 (53)	53.86 (29)	53.59 (14)	50.24 (7)
Tapping test non-dominant hand	Scores are given as the average number of taps in 10 seconds						
Men	Primary school	57.01 (98)	53.98 (56)	51.72 (234)	49.59 (243)	45.96 (186)	43.72 (128)
	Secondary school	58.52 (106)	55.41 (49)	53.78 (171)	51.59 (139)	47.37 (92)	47.17 (76)
	High school/College<4y	58.41 (76)	56.17 (45)	56.61 (100)	57.58 (71)	51.47 (56)	47.54 (29)
	College/university ≥4y	61.84 (36)	55.59 (20)	57.40 (71)	58.75 (24)	51.09 (24)	45.79 (13)
Women	Primary school	50.47 (63)	48.26 (249)	46.94 (376)	44.45 (313)	42.57 (318)	38.06 (217)
	Secondary school	53.87 (96)	49.75 (125)	49.78 (158)	48.09 (98)	44.46 (107)	40.81 (36)
	High school/College<4y	56.30 (97)	53.56 (71)	56.85 (65)	48.62 (50)	47.49 (38)	46.16 (18)
	College/university ≥4y	55.13 (49)	53.12 (42)	50.99 (53)	47.98 (29)	47.97 (14)	44.33 (7)

Paper II - Carotid atherosclerosis predicts lower cognitive test results: A 7 years follow-up study in 4371 stroke-free subjects. The Tromsø Study.

In this paper we studied the association between ultrasound-assessed carotid atherosclerosis and cognitive test scores after 7 years follow-up in stroke-free subjects. Atherosclerotic plaques were found in 40.7% of women and 49.6% of men. In the multivariable analyzes adjusted for sex, age, education, depression and vascular risk factors, plaque presence was significantly associated with lower test scores on the verbal memory test (p=0.01) and on the digit-symbol coding test (p=0.03). The number of plaques (p=0.01) and the total plaque area (p=0.02) were associated with lower scores on the verbal memory test. The mean total IMT was negatively associated with the digit-symbol coding test, but CCA-FW-IMT did not show any association with the cognitive tests. There were no independent associations between the carotid ultrasound variables and the tapping test.

Paper III - Carotid artery plaque progression and cognitive decline. The Tromsø Study 1994-2008.

The aim of the study was to assess if progression of carotid atherosclerosis in stroke-free subjects was associated with lower cognitive test scores and cognitive decline. From Tromsø 4 to 5, the prevalence of plaques increased from 44.5 % to 61.0 %, the average total plaque area increased from 8.7 mm^2 to 14.8 mm^2 and there was a shift toward a higher number of plaques. In all cognitive tests we observed a small decline in test results over the 6 years from Tromsø 5 to 6. In multivariable regression models adjusted for sex, age, education, depression and vascular risk factors, the average of Tromsø 4 and 5 measurements of number of plaques and total plaque area were associated with lower scores on all cognitive tests ($p \leq 0.02$) in Tromsø 5. Progression of both plaque number and total plaque area were independently associated with lower scores on the digit-symbol coding test ($p \leq 0.04$) and the tapping test ($p \leq 0.03$), but not on the verbal memory test. In the subgroup followed with cognitive retesting in Tromsø 6 no association was found between plaque scores and decline in cognitive test scores.

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

The major strengths of this study are the large sample size, the prospective design, relevant adjustment variables and the use of repeated and standardized measurement of carotid ultrasound and cognitive tests sensitive to cognitive decline in a general population (52, 55). To our knowledge no other population-based studies have examined the progression of carotid atherosclerosis in relation to cognitive function.

The study design also has some limitations. We had no information of cognitive function at baseline, and could therefore not be certain of the temporal association between risk factors and cognitive test scores. Nevertheless, the independent variables were assessed 7 years before cognitive testing, and this combined with knowledge from previous prospective studies, indicate that the risk factors are predictors of lower cognitive test scores and not the opposite (23, 31).

The three cognitive tests used in this study were chosen for their feasibility in the setting of a large population study with a large number of participants who also went through a considerable number of other clinical and laboratory tests. The tests do not give a total picture of an individual's cognitive function, and interpretation of results is restricted to the cognitive domains studied. The study did not include validated tests for dementia or MCI, and no validated cut-off limits for cognitive impairment existed for the cognitive tests used. However, Mini-Mental State Examination (MMSE) was added to the cognitive test battery in Tromsø 6, but was not used in this study because no follow-up data were available for this test. Outcome measures were cognitive test scores, either assessed as continuous variables or comparing scores in the lowest quintile with the other four. A more comprehensive cognitive test battery with validated cut-off

limits for cognitive impairment or dementia would have strengthened the study and made clinical interpretations easier.

Examination of only the right carotid artery may be a limitation, as inclusion of the left carotid artery might have given a better description of the individual total carotid plaque burden. The side of which carotid atherosclerosis occurs may affect cognitive tests results differently. Previous epidemiological and clinical studies have found that left carotid stenosis, in contrast to stenosis on the right side, is more strongly associated with lower performance on cognitive tests involving language and on Modified MMSE (31, 56), and also with progression of AD assessed by MMSE (57). However, in Paper II we found that both high number of plaques and total plaque area at baseline were associated with lower scores on the verbal memory test after 7 years follow-up, and the average plaque scores between baseline and follow-up were associated with scores on all cognitive tests. MRI imaging of the cohort would have added valuable information to the interpretation of our results regarding the role of vascular mechanisms.

5.1.2 Internal validity

Selection bias

High participation rates and no predefined selection criteria for invitation other than birth year and being a resident of the municipality of Tromsø, minimized the chance of selection bias in Tromsø 4-6. Detailed analyses of mortality or morbidity according to attendance have not been possible because of legal restrictions. However, subjects who were consistent attendees demonstrated a lower mortality than subjects who attended only one of the surveys (47). Both the exposure (carotid atherosclerosis) and the outcome variables (cognitive test scores) may have been subject to selection bias. Participants with the most advanced atherosclerosis could be less likely to attend the follow-up studies due to cardiovascular disease or death. We have no information on cognitive function of those who did not meet, but a selection towards lower

participation rate among persons with cognitive impairment and dementia both at baseline and at follow-up would be expected. Though invited, institutionalized persons were probably not able to appear at the location of the survey or to complete the comprehensive screening battery. Selection of subjects in the data collection process has probably occurred, as 561 more subjects completed the tapping test than the digit-symbol coding test in Tromsø 5. It is likely that the proportion of subjects with cognitive impairment was higher among those who did not complete all tests. All these sources of selection bias have probably affected the overall rate of decline in cognitive test scores from Tromsø 5 to 6, as the average decline was approximately as could be expected as an effect of age alone (Table 1). This may have precluded the possibility to find associations between risk factors and cognitive decline.

Information bias and misclassification

Information bias occurs when measurement of either the exposure or the outcome variables is systematically inaccurate. In cohort studies, misclassification of exposure variables is often non-differential (not dependent of the outcome variable), and usually attenuates or underestimates the effect estimate. The problem of information bias has been addressed in the Tromsø study in general by having test personnel that are not directly involved in the scientific project and thereby not biased by scientific hypothesis in their measurement. Standard protocols and standard operational procedures contributed to minimizing errors. In this study, information on smoking, disease, use of medication and depression was obtained from self-administered questionnaires. Such information is likely to be inaccurate and a source of information bias (58). In a previous validation study on self-reported stroke based on questionnaires from participants in Tromsø 4, the positive predictive value was 0.79, sensitivity 80% and specificity 99% (59). To avoid misclassification, we used the Tromsø study end-point registry for assessing strokes in Paper II and III and found more stroke cases than was self-reported. The sensitivity of self-reported diabetes is found to be moderate in other studies (60, 61). To increase sensitivity, diabetes was defined as self-reported diabetes and/or

regular use of insulin or oral antidiabetics. We used current daily smoking as a predictor in this study, as data on previous smoking habits are prone to recall bias and did not add any new information to the analyses. Previous studies on the serum concentration of thiocyanate in smokers and non-smokers have supported the validity of the responses to the question on smoking (62, 63). Answers to the questions regarding physical activity were in a previous study found to have an inverse dose-response relationship with BMI and smoking (64). Assessment of depression could have been more accurate if we had used a standardized depression scale (for example MADRS). Blood samples were of practical reasons assessed non-fasting. Regarding total-cholesterol, fasting or eating before blood collection does not have a marked effect on measurements (65).

Reproducibility of ultrasound measurements was found to be acceptable (34, 49, 50). In Paper III we found that the average measurement of plaque scores in Tromsø 4 and 5 was associated with lower scores on all cognitive tests, whereas baseline plaque scores or the change in plaque scores were not consistently associated with all tests. An alignment of measurements errors with use of the average plaque scores could make the average scores a more robust exposure variable.

Confounding

A confounder is an independent risk factor for the outcome variable that is also associated with one or more of the exposure variables of interest. Confounding could lead to under- or overestimation of the association studied. We adjusted for known confounders such as sex, age, education, depression and vascular risk factors. We did not measure the APOE gene, where the ε4 allele has been found to be a major risk factor for AD. The presence of one copy of the APOE ε4 allele increases the risk of late-onset AD by about three times and two copies by about 12 times, but presence of the APOE ε4 is neither necessary nor sufficient for developing the disease (66). Several studies have found an association between the ε4 allele and higher carotid IMT, and although significant results have not always been found (67), APOE ε4 may be a

confounder in the relationship between carotid atherosclerosis and cognitive test results.

Excessive alcohol drinking is a risk factor for cognitive impairment, but some studies have found that low or moderate alcohol consumption, especially wine consumption, may protect against cognitive decline (68, 69). In a previous paper from the Tromsø study, we found that moderate wine consumption was independently associated with lower cognitive test scores after 7 years follow-up (70). Moderate alcohol consumption may also lower the risk of atherosclerosis (71) and be a possible confounder for the relationship between atherosclerosis and cognitive test results. Adjustment for alcohol consumption in our study did not change estimates of the association between atherosclerosis and cognitive test scores and were therefore not included in analyzes.

5.1.3 External validity

External validity refers to the generalizability of results and applicability to other populations. Selection criteria for participation in the Tromsø study were age and residency in Tromsø, and the Population Registry of Norway was the source for the invitations. All age groups of interest were studied and the risk factor levels of the Tromsø population are compareable to other Western populations. Our results are therefore probably applicable to other Western populations, however, generalizability could be restricted by ethnicity, as the Tromsø population mainly are Caucasians. Associations between vascular risk factor, atherosclerosis and cognitive test scores are restricted to the cognitive domains studied.

5.1.4 Statistical considerations

Although we found statistically significant predictors of cognitive test results the magnitude of the effects observed were probably modest. Estimation of the statistical power needed for showing a possible clinical relevant difference or change in cognitive test scores was not possible because no validated cut-off limits for the cognitive test

scores existed. In Paper I, we divided cognitive test scores in quintiles to estimate risk difference between participants scoring in the lowest quintile compared to the upper four, but we don't know if this cut-off represents a clinical meaningful limit.

5.2 Discussion of main results

5.2.1 Cardiovascular risk factors and cognitive test results

Diabetes, smoking, and systolic blood pressure were independent predictors for lower cognitive performance after 7 years of follow-up in both men and women, and physically active women had lower risk of low cognitive test scores.

Diabetes showed the strongest negative relationship to cognitive test scores in both genders with a 3 fold increased OR of scoring in the lowest quintile on the verbal memory test in men, and a 2 fold increased OR on the tapping and digit-symbol coding tests in women. This is in line with observations from previous population-based studies (23, 42, 72).

Whereas some earlier studies found no association and even positive associations between smoking and cognitive function (23), recent prospective studies have found negative associations between smoking and cognitive function (73). This is supported by our study. The negative effect of smoking may be more pronounced in those not carrying the APOE ε4 allele (74).

Systolic blood pressure was negatively associated with cognitive performance and hypertensive women had an increased risk of lower cognitive test scores. This is in line with some previous cohort studies (23). Other studies found no association (75), and some have indicated a U-shaped association between blood pressure and cognitive function (76). Methodological differences between studies, such as the age at assessment of blood pressure and of cognitive function, different cognitive domains

studied and the length of follow up, may be some of the reasons for the conflicting results (77, 78). A recent Cochrane review of four randomized controlled trials on blood pressure treatment in prevention of cognitive impairment and dementia showed no overall benefit of treatment (79). The high average age of 75.4 years of participants and the relatively short mean follow-up time of 5 years in these studies may have caused the negative results. While the impact of late-life hypertension is unclear and even may be a result of cognitive decline, several studies have shown that mid-life hypertension is a risk factor for cognitive decline in late life (78, 80).

Previous studies on the relationship between physical activity and cognitive function are conflicting. Reduced risk of dementia was found in a 21 years follow-up study in physical active men and women (81). In a 5-year follow-up study of 4615 men and women aged 65 and above, physical activity protected against cognitive impairment and Alzheimer's disease only in women (82). Other studies have found no association between physical activity and cognitive function (83). Physical activity may prevent vascular damage and protect against cognitive decline through a number of possible mechanisms. Physical activity reduces blood pressure, cholesterol level, BMI and prevents development of diabetes. Influence on brain plasticity, angiogenesis, synaptogenesis, neurogenesis, and increased levels of neurotrophic factors may also play a role in the association of physical activity and cognitive function (84). Exercise is found to significantly reduce the amount of amyloid-β (Aβ) plaques in transgenic mice (85). The results of our study may indicate a better preventive effect of physical activity on cognitive testing in women than in men. Interactions between exercise and hormone metabolism might contribute to sex differences. However, the effects are small with partly overlapping confidence intervals between genders and should be interpreted with caution.

No association was found between serum total-cholesterol, HDL-cholesterol or coronary heart disease and cognitive test scores in any of the regression models. The lack of association between cholesterol and cognitive function is surprising given the strong

association between cholesterol and large vessel atherosclerosis which can increase the risk of vascular dementia. Furthermore, cholesterol reduces amyloid precursor protein alpha, increases cerebral β-amyloid peptide generation and could thereby increase the risk of AD (86). Some cohort studies of ageing populations found no effect (23) and even protective effects of cholesterol (87), but a study on 40-45 years old subjects found that increasing cholesterol levels increased the risk of both vascular dementia and AD three decades later (88). In two reviews, total-cholesterol measured in mid-life, but not in late life where a risk factor for dementia (89, 90). Randomized controlled trials on treatment of cholesterol with statins in the prevention of dementia or cognitive decline with 3-5 years follow-up were negative (86). The negative results in these studies may have been influenced by the relative short period of follow-up. The lack of association found for lipids in contrast to associations found for diabetes and hypertension in our study, may be due to a greater effect of small vessel, rather than large vessel disease on early cognitive impairment. Small vessel disease could particularly affect subcortical circuitry and thereby executive function which can be revealed by impaired digit-symbol coding test scores. MRI manifestations of cerebral small vessel disease are thought to develop gradually from white matter lesions (WML) to leucoaraiosis and lacunar infarcts. WML have been found to increase the risk of dementia (91, 92).

At the time when Paper I was written, data on cognitive test scores in Tromsø 6 and cognitive decline from Tromsø 5 to 6 were not ready. In supplementary analyses made when data on cognitive decline was available, no consistent associations were found between baseline vascular risk factors and cognitive decline in multivariabel regression analyzes adjusted for sex, age, education, depression, systolic blood pressure, total-cholesterol, HDL-cholesterol, body mass index, current smoking, physical activity, diabetes and coronary heart disease in 2467 subjects with complete baseline data of vascular risk factors and data on cognitive decline from 7 to 13 years of follow-up. Age was a consistent predictor of cognitive decline on the digit symbol coding test and the tapping test. Subgroup analyses of those in the highest quartile of decline did not add

new information (data not shown). Selection bias may have precluded our possibility to detect associations between vascular risk factors and cognitive decline, as discussed in the chapter of internal validity on page 32.

5.2.2 Carotid atherosclerosis and cognitive test results

In Paper II, the mean total IMT at baseline predicted lower score on the coding test after 7 years of follow-up, but as plaques were included in our IMT measurements, the association between mean total IMT and cognitive test scores is probably largely dependent on plaque formation. The lack of association with CCA-FW-IMT further underlines this, as plaques are infrequent in this segment.

The presence of carotid atherosclerotic plaques at baseline predicted lower scores on the verbal memory test and the digit-symbol coding test after 7 years of follow-up, but baseline scores of the number of plaques and the total plaque area only predicted lower scores on the verbal memory test. In paper III we found that the average plaque scores of measurements at baseline and 7 years follow-up were associated with lower scores on all cognitive tests. Progression of plaque scores was associated with lower scores on digit-symbol coding test and tapping test. Thus, average plaque scores may seem like better predictors for cognitive test results than change in plaque scores or baseline plaque scores. This could be due to measurement errors in assessing a one-time measurement or change in measurements, whereas an average score may align these errors.

Progression of total plaque area and plaque number was not associated with lower scores on the verbal memory test. As noted previously in the discussion of study design, carotid atherosclerosis in the left carotid artery is more strongly associated with lower performance on cognitive tests involving language (56), and this could be one reason why no association was found. However, the average plaque scores between baseline and follow-up were associated with scores on all cognitive tests.

In supplementary analyses of average plaque scores and progression of plaque scores from baseline to 7 years of follow-up and cognitive test results after 13 years of follow-up in 2081 subjects, the estimates of the effect of plaque scores on cognitive test result did not considerably differ from those found at 7 years of follow-up. Significant results were found for the association between average plaque scores and scores on the verbal memory test and the digit-symbol coding test, but not for the other analyses, probably reflecting less power to detect significant associations in this cohort than in the cohort tested at Tromsø 5.

We found no association between carotid atherosclerosis and cognitive decline. This apparent inconsistency could be due to several factors. The large loss to follow-up on cognitive testing in Tromsø 6 makes interpretations of results on cognitive decline difficult. Selection bias has probably occurred as those with poor cognitive function either did not attend Tromsø 6 or could not complete all cognitive tests. Those with repeated cognitive testing were younger and had a better vascular risk factor profile than those who only attended cognitive testing in Tromsø 5 (Table 1 in Paper III). The prevalence of cognitive decline and dementia increases mainly from the age of 70, which was the mean age at the second cognitive testing, and may explain why cognitive decline were modest also in those who participated (3). A 7-8% decline in test scores on the verbal memory test and the tapping test was found, but this is not much more than the expected effect of aging (Table 1). The decline observed in scores on the digit-symbol coding test was less than expected, and could be caused by measurement errors. Larger within-person variance of repeated measurements than of single measurement of both atherosclerosis and cognitive tests can be expected to result in stronger estimates for single measurement analyses compared to measurement of progression. Lower statistical power in the smaller subgroup with cognitive retesting combined with modest effects of carotid atherosclerosis on cognitive test scores may have influenced the lack of association.

No other population-based studies have examined the progression of carotid plaques in relation to cognitive test results. The associations found between both the average of Tromsø 4 and 5 carotid plaque scores and progression of carotid plaque scores and lower cognitive test results in Tromsø 5 are in line with results from some previous epidemiological studies that have assessed the impact of a one-time measure of atherosclerosis on cognitive function. One cross-sectional study found that subjects with carotid stenosis (≥ 35%) performed weaker on cognitive tests than subjects without stenosis (43). In a large cohort study, a high-grade stenosis (≥75%) in the left carotid artery at baseline was a significant predictor of cognitive decline. The results were independent of vascular changes on brain MRI (31). Several population-based studies of elderly subjects (>65 year) have found associations between carotid IMT in the CCA and ICA and subsequent cognitive decline (41, 42), but conflicting results were found in middle-aged populations. Two large cohort studies found no association between baseline mean carotid IMT and cognitive decline after 6 and 14 years of follow-up (23, 44), whereas one study found that mean carotid IMT at baseline was associated with poorer cognitive test performance after 4-years, independent of MRI markers of silent cerebral infarcts or white matter hyperintensities (32). Our findings add to the results from the last study, indicating that atherosclerosis in middle age is a risk factor for lower cognitive function in later life.

In the Rotterdam study, the number of carotid plaques was associated with dementia in cross-sectional analysis (22), but this could not be confirmed in a later prospective study (46). However, a significant negative trend was found between number of carotid plaques and a combined endpoint of dementia and mortality, suggesting that higher mortality rate in subjects with carotid plaques may have attenuated a possible association between plaque number and dementia. The risk of AD was increased in the highest quintile of CCA-IMT compared with the lowest quintile (hazard ratio 1.54, 95% CI 1.03-2.30) after 9 years follow-up in 5399 subjects, but carotid plaque number at

baseline did not predict dementia (46). Similar results were found in the Cardiovascular Health Study (CHS) were the highest quartile of baseline IMT in the CCA and ICA, but not carotid stenosis, was associated with increased risk of AD (45). One clinical study of 66 patients with AD found that the progression of carotid plaques over 12 months correlated with increased cognitive impairment (93).

Several possible mechanisms may explain an association between carotid atherosclerosis and lower cognitive test scores. Individuals with a confirmed stroke were excluded in this study, but embolisms from carotid atherosclerosis could cause silent strokes. Results from the population-based Rotterdam Scan Study showed that the presence of silent brain infarcts on MRI more than doubled the risk of dementia after 3.6 years follow-up (94). Carotid atherosclerosis may also act as a marker of intracerebral atherosclerosis, cerebral small vessel disease, or microangiopathy with reduced intracerebral perfusion as a result. Small vessel disease and MRI detectable white matter lesions have been associated with cognitive decline (91). However, three population-based studies found significant associations between carotid stenosis and reduced cognitive function independently of lesions detected on brain MRI (31, 32, 43). Theoretically, neuropsychological test results could be more sensitive to microembolic lesions than MRI. Cerebral hypoperfusion due to high-grade stenosis (>70%) could be a possible mechanism for lower cognitive scoring, but as the prevalence of high-grade stenosis in the general population is low, this is an unlikely explanation in our study (95).

In addition to the possible effect of carotid atherosclerosis on silent ischemic cerebral lesions, the association between carotid atherosclerosis and cognitive test results could be mediated through AD pathology, as cases with mild cognitive impairment due to preclinical and early AD probably were included in the cohort. The association between carotid intima-media thickening and AD found in two studies (45, 46) may reflect two independent pathological processes that share the same risk factors such as high blood pressure and smoking (96), or that vascular changes play a role in the pathogenesis of

the disease (26). In the Rotterdam study, adjustment for cardiovascular risk factors did not attenuate the association between IMT and AD (46). Two large autopsy studies found no association between cerebral vascular lesions and the two hallmarks of AD, amyloid plaques and neurofibrillary tangles in individuals with AD, indicating no causative but maybe an additive effect of vascular lesions on AD (97, 98). Three large autopsy studies found a strong association between the degree of intracranial atherosclerosis and Alzheimer pathology (17, 98, 99), whereas one study found no association (100). Low ankle-arm index was significantly associated with increased risk of AD, indicating that generalized atherosclerosis could be a risk factor for AD (45). The mechanisms for a possible associations between atherosclerosis and AD are still unclear, but cerebral hypoxia could possibly destabilize neurons and contribute to a neurodegenerative process characterized by formation of neurofibrillary tangles and amyloid plaques (26).

6. Conclusions and implications for further research

We found that diabetes, smoking, hypertension, physical inactivity and the presence of carotid plaques at baseline predicted lower scores on cognitive tests after 7 years of follow-up. Progression of plaque scores from baseline to 7 years of follow-up was associated with lower scores on cognitive tests at follow-up. No associations were seen between vascular risk factors, carotid atherosclerosis and cognitive decline.

Results from this study suggest that diabetes, smoking, hypertension, physical inactivity and carotid atherosclerosis could be targets for preventive efforts to delay cognitive impairment, but as no associations were found between risk factors and cognitive decline, interpretations should be made with cautiousness.

Effect estimates from other epidemiological studies indicate that modification of vascular risk factors could have a great impact on prevention of dementia (101), and

clinical studies have found that intensive treatment of vascular risk factor could delay progression of atherosclerosis (35, 102). However, intervention studies on blood pressure and lipid lowering treatment in the prevention of dementia and cognitive impairment have so far been disappointing (79, 86). Negative results in intervention studies may have been caused by small sample size, short periods of follow-up, and that study-subjects already were in a prodromal phase of dementia and had passed the time-window for prevention (103, 104).

There is a need for future studies with long time follow-up to further explore how vascular risk factors and atherosclerosis affects the risk of cognitive impairment and decline. We need more knowledge about how the length of exposure and the age at exposure to risk factors affect cognitive decline, and whether an optimal time-window for preventive strategies exists. Little is also known about whether cut-off levels exist for when risk factors affects cognitive decline and if relations are linear or not. Population studies that assess how medications used for treating vascular risk factors and atherosclerosis affect cognitive decline could give valuable information for designing new intervention studies. To further explore the pathophysiological mechanisms of how atherosclerosis and vascular risk factors affects cognitive function, brain MRI and genetic testing of APOE should be included in the test battery.

A major concern in the interpretation of our study was the great loss to follow-up from Tromsø 5 to 6 and the lack of cut-off values for clinically important low scores on the cognitive tests. In future studies, the cognitive tests should be validated against criteria for mild cognitive impairment. The problem of loss to follow-up could partly be solved by ambulatory screening procedures in the homes of participants or at nursing homes. However, ethical aspects of such recruitment strategies would need careful consideration.

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Paper I

Paper II

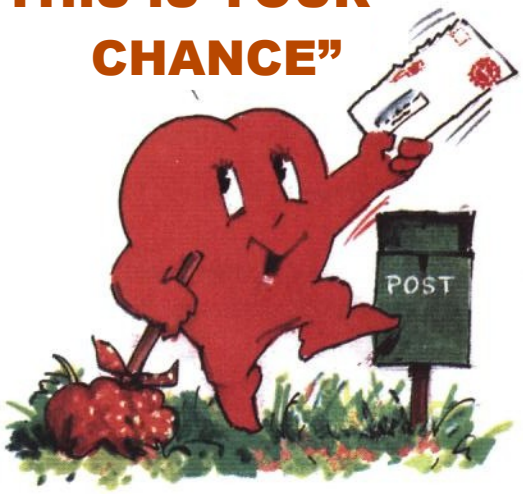
Paper III

Appendix A

Questionnaire 1
Tromsø 4, 1994-95
English version

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 B

Questionnaire 2 (<70 years)
Tromsø 4, 1994-95
English version

The Tromsø Health Survey

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

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

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

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

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health Screening Service

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

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

Day Month Year

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

CHILDHOOD/YOUTH

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

..... 24 - 28

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

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

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

How many of the first three years of your life

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

How many of the first 15 years of your life

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

HOME

Who do you live with?

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

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

What type of house do you live in?

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

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

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

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

What is the main source of heat in your home?

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

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

WORK

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

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

Can you decide yourself how your work should be organised?

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

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

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

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

YOUR OWN ILLNESSES

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

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

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

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

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

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

ILLNESS IN THE FAMILY

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

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

SYMPTOMS

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

How often do you suffer from sleeplessness?

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

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

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

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

How often do you suffer from headaches?

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

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

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

USE OF HEALTH SERVICES

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

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

MEDICATION AND DIETARY SUPPLEMENTS

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

Medicines

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

Dietary supplements

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

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

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

FRIENDS

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

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

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

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

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

FOOD HABITS

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

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

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

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

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

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

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

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

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

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

ALCOHOL

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

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

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

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

WEIGHT REDUCTION

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

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

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

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

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

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

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

Your comments:

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

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

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

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

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

If you still menstruate or are pregnant:

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

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

PREGNANCY

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

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

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

If "Yes", during which pregnancy?

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

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

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

CONTRACEPTION AND ESTROGEN

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

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

376 .....

If you use or have ever used oral contraceptive pills:

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

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

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

If you have stopped taking the pill:

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

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

The Tromsø Health Survey

Appendix C

Questionnaire 2 (≥70 years)
Tromsø 4, 1994-95
English version

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

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

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

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

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

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø

Statens helseundersøkelser

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

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

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

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 -28

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

Hvordan var de økonomiske forhold i familien under din oppvekst?

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

Hvor gamle ble dine foreldre?

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

BOLIG

Hvem bor du sammen med?

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

Hvilken type bolig bor du i?

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

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

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

TIDLIGERE ARBEID OG ØKONOMI

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

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

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

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

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

Hva slags pensjon har du?

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

Hvordan er din økonomi nå?

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

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?

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

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

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

EGNE SYKDOMMER

Har du noen gang hatt:

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

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

Har du eller har du hatt:

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

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

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

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:

Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

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

SYMPTOMER

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

Hvor ofte er du plaget av søvnløshet?

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

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

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

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

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

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

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

LEGEMLIGE FUNKSJONER

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

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

Er du avhengig av noen av disse hjelpemidlene?

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

BRUK AV HELSEVESENET

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

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

Har du hjemmesykepleie? ..... ❑ ❑

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

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

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

LEGEMIDLER OG KOSTTILSKUDD

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

Legemidler

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

Kosttilskudd

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

FAMILIE OG VENNER

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

Hvis "Ja": Hvem kan gi deg hjelp?

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

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

	Ja	Nei
Føler du at du har nok gode venner? 299	❑	❑

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

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

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

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

KOSTVANER

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

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

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

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

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

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

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

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

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

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

TRIVSEL

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

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

Hvordan ser du på livet fremover?

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

BESVARES BARE AV KVINNER

MENSTRUASJON

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

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

SVANGERSKAP

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

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

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

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

Hvis "Ja", i hvilket svangerskap?

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

ØSTROGEN-MEDISIN

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

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

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

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

Appendix D

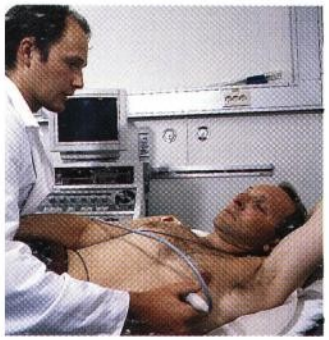
Invitation to Tromsø 4
2nd visit, 1994-95
English version

YOU ARE INVITED TO THE SPECIAL STUDY

The health study in Tromsø invites some of the participants for a free special study.

The special study

The Special Study uses advanced technology which makes images of blood vessels and the heart, and provides information on skeletal structure and fatty tissue. X-ray technology is not used, but rather ultrasound or light-waves which are reflected against a small device held to the skin (pictured). These tests do not penetrate the skin, are not painful and have no known side-effects. The Special Study also involves blood- and urine samples, as well as registering heart activity (ECG).



Why are you invited?

We do not have the opportunity to offer the Special Study to everyone. We invite all men and women born between 1920 and 1939 and some randomly picked from other age-groups.

What is the purpose?

Many diseases evolve gradually over long periods of time without people's awareness, but with advanced methods it is possible to detect changes early. In certain cases prevention or treatment can be initiated even before the disease develops. In other cases we are not sure what the changes signify and further research is necessary. The Special Study is therefore a unique offer which not only has value to you personally; the results are used in medical research which breeds increased knowledge about how diseases initiate and how they can be prevented and treated.

The Special Study involves

✓ Ultrasound of blood vessels and the heart

The arteries in the neck and stomach are studied. This gives information whether the arteries are clogged or whether they are diluted/contracted. The shape of the heart and its functionality is looked at in 50 per cent of the participants.

✓ Study of bone density and amount of fat

The measurements are used to determine risks of osteoporosis and fractures, and whether there is a correlation between body fat and disease.

✓ ECG

ECG is registering heart activity which also provides information concerning heart disease.

✓ Urine sample

The urine samples are used to indicate kidney function through measuring the amount of protein and creatinine substances. The result is most accurate if urine from the separate days are examined.

✓ Blood sample

Blood samples are examined for fatty substances and substances which indicate how the kidneys work, metabolism (calcium and sugar) and blood clotting. The blood sample is frozen so it can be used for later research.

✓ Further follow up

- If we think further examination or treatment is required, it will be offered to you.
- Some participants may be asked to take part in later studies for further research.

THE SPECIAL STUDY · 94 – 95

Practical information

Place and time

The examination will take place in the second floor at Elisabeth center; the old maternity hospital (Mellomveien 50) - at the floor above the Tromsø study. The examination takes 1 to 1.5 hours and is free of charge.

We hope you can use the time appointed.
Date and time is given in the brochure. If you need to change appointment, we ask that you notify us by calling 77 64 59 00

Urine sample

You have been given three urine glasses marked 1, 2 and 3. We wish that you take a morning urine sample in each glass in the last three days before the special study. You have therefore got a glass for every morning. Note the following:

1. Please urinate a small amount of urine in the toilet before you take the urine sample. Last morning sample is taken on the day you come to the survey.

2. State the date on each urine glass.

3. It is an advantage if samples can stay cold.

4. Deliver all three glasses when you come to the survey.

Use of medicine

On the next page please make a note which medications you've used the past week. This can be important when interpreting the results.

Clothing

Because of the blood pressure measuring, we ask you to wear clothes that are not tight on the arm. When examining the heart, it is necessary to undress the upper body. At examination of the aorta some clothes must be pulled down so that the abdominal region is exposed.

About consent

The information about you will be treated confidentially. The information will be stored and used according to the rules set by the Data Inspectorate and Norwegian law. The study has been recommended by The Regional Committee for Research Ethics. Should further examinations be required, we ask your consent to forward relevant data to your doctor or the Regional Hospital in Tromsø. We also request that you upon arrival give your consent to:

- ✘ that we forward your results to your doctor or the Regional Hospital in Tromsø if you need further examination.
- ✘ that your results may be used for medical research through combining them with other health- and disease registries as well as information from previous health studies in Tromsø. Prior to analysing the results your name and social security number will be removed.
- ✘ that your blood sample may be stored and used for medical research.
- ✘ that the Health Examination in Tromsø may contact you later with a request to participate in other studies.

Even if you give your consent now, you may later reconsider and deny the use of your results.

The special study

is part of the health survey in Tromsø, and organized by the University of Tromsø, Faculty of Medicine in cooperation with the Regional Hospital in Tromsø

UNIVERSITETET I TROMSØ

Use of medicine

To interpret the results we want information about medication use in the last week. Please state name, strength and dose of all medications that you are using. If in doubt about filling, bring the drugs. We will then be able to help you.

Name of medicine	Strength	Dose
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

Welcome

THE SPECIAL STUDY '94 – 95

SPESIALUNDERSØKELSEN '94 - 95

You are invited to the special study in Tromsø

LUNDBLAD GRAFISK AS, TROMSØ

Appendix E

Protocol for ultrasound measurements

Tromsø 4 and 5

English version

PROCEDURES FOR MEASUREMENTS OF INTIMA-MEDIA THICKNESS AND RECORDING AND MEASUREMENTS OF PLAQUE OF THE RIGHT CAROTID ARTERY. THE TROMSØ-STUDY 1994/95 AND 2001

by Oddmund Joakimsen
Revised March 2001

1. The Acuson ultrasound instrument is switched on.

2. A videocassette is inserted in the video recorder.

3. Check that the videotape has been wound to the right position, do not overwrite previous recordings. The videocassette should not be removed from the recorder during the day.

4. Cassettes are marked with serial numbers, uneven numbers for Acuson I, even numbers for Acuson II.

5. The initials and the identity numbers of the participant and the sonographer number (Einar = 1, Stein Harald = 2, Technician = 3) are written on each ultrasound image recorded. Labels with the ID-number of the participants are attached to the registration form, in which all ultrasound data obtained from the participants are filled (plaque localization, size, "missing measures" coding, etc.).

6. A RES-field, appropriately adjusted to a maximum width of the screen and a depth of a little more than the preset size (> 2 cm) is positioned on the screen (This makes off-line calibration easier).

7. The subject is examined in a supine position with the head slightly rotated to the left (15-45 degrees). ECG-pads are attached to both arms and the right leg (or abdomen) (lead I), and the right carotid is insonated by a 7.5 MHz ultrasound transducer.

8. The examination starts with identification of crossectional B-mode images of the carotid artery, and, if necessary for identifying purposes in combination with colour-Doppler and/or pulsed wave Doppler 5 MHz. The examination starts caudally in the neck, normally just above the clavicle, then moving the probe upstream with simultaneous rotation movements to search for plaques also at the circumference of the vessel. Thus, the carotid artery is searched from the proximal part of the common carotid artery (CCA), upstream to the bifurcation (BULB), and as far up in the internal carotid artery (ICA) as technically possible. A PLAQUE is defined as a presumed atherosclerotic lesion of the intima layer of the vessel wall presenting a focal protrusion of more than 50% of the intima-media thickness (IMT**)** of the surrounding vessel wall, often with deviating echogenicity compared to other part of the artery wall. Whether a plaque is present or not is a decision taken by the sonographer during the examination. Live crossectional imaging of the whole carotid artery is recorded on the videotape.

9. An ultrasound examination sequence is then performed in the TRIPLEX -mode (i.e., combination of B-mode examination, pulsed wave Doppler, colour Doppler) 3-4 cm proximally to the bifurcation and upstream 2-3 cm distally the bifurcation in the ICA. The objective of this part of the examination is to look for stenotic areas along the artery that causes hemodynamic disturbances. However, if plaques later during the B-mode scanning procedure are found suspicious of a hemodynamic significant stenosis, a new TRIPLEX examination is performed to re-evaluate the flow conditions. A LIVE TRIPLEX-sequence of the relevant part of the carotid artery is recorded on the videotape if a stenosis is suspected.

10. B-mode longitudinal ultrasound scanning of the carotid artery is then performed. To get an optimal topographic reference, the examination is starting as proximally as possible in CCA. The probe is then moving upstream with simultaneous rotating movements to look for plaques in all segments, both the near and the far wall. If a plaque is found, a frozen image of the vessel-wall is taken – either directly by using the "FREEZE"- key, or by choosing on of the pictures from the cine-loop. It is important that the plaque is presented as distinctly as possible and after the guidelines according to elementary ultrasound principles such as vertical propagation of the ultrasound beam, presentation of the plaque in the full diameter of the vessel and not in chord, not cutting the plaque skew causing a falsely too large thickness of the plaque. To ensure the quality of plaque registration, some technical points may be of help: The plaque should be "attached" at its both ends to the typical double-lined intima-media structures visible on the B-mode image, and these double-lined structures should best be visible both in the near and the far wall at the same time. When the echogenicity obtained is as high as possible (as bright as possible), this is an indication that the ultrasound waves have cut the plaque optimally. An electronic calliper is put on the top of the plaque (at the interface between the surface of the plaque and the vessel lumen), and another calliper in the presumed transition zone between the media and the adventitia layer. The distance between the callipers is the thickness of the plaque, and that value is put on the registration form in the appropriate box. The B-mode image of the plaque is identified correctly by marking on the display what has been found, and where: PLAQUE ICA FW (a plaque in the far wall of the internal carotid artery), PLAQUE BULB NW (a plaque in the near wall of the bifurcation), etc. A short recording of approximately 5 sec. is videotaped. If more than one plaque is present at a site (e.g., in the far wall of ICA), the largest is chosen and recorded.

    After identifying and recording of plaques, imaging procedures to get optimal measures of IMT from CCA and the BULB are performed. Optimal images are available when distinct double contours of the vessel wall typical for the intima-media complex can be seen. It is important that the longitudinal axis of the insonated vessel wall is perpendicular to the ultrasound beam direction. To avoid falsely too thick intima-media layer, the IMT should be measured in the full diameter of the artery and not in a chord. When satisfactory images are achieved, R-wave triggered IMT-registrations are recorded on a cine-loop containing more than 20 images. Afterwards, the images stored in the cine-loop are scrutinized and 3 of most representative images, and each at least 10 images apart, are selected for recording on the videotape.

    Regarding IMT measurements in the BULB, the start of the BULB is first identified and then marked with an arrow. This is the point where the parallel walls of the CCA are starting to diverge. If the probe throughout the recording process in the cine-loop has changed position, the placing of the arrow marker must be adjusted accordingly. It is important to underline that it is the sonographer who places the marker and not the off-

line reader of the IMT-measurements. The arrow setting has to be as precise as possible, particularly when a plaque is located in the border zone between BULB and CCA to avoid over-or underestimating of IMT.

The target site for IMT measurements of BULB is the 1 cm area from the start of the BULB and upstream, distally. If only a part of this distance is measurable, a recording may, however, be performed on this shorter distance if the live sequence shows that this part of the vessel wall is representative of the rest of the 1 cm area. This shorter, measurable distance is marked with an electronic star. The 3 chosen images are marked BULB1, BULB2 and BULB3 and recorded on the videotape. If no measurable image is possible to obtain, an image from the BULB is still recorded and marked MB, i.e., "missing bulb". IMT measurements from the near wall of the BULB are not performed.

11. Then a B-mode scanning of the CCA is performed, starting at the BULB and downstream as far as possible. Registration and measurements of plaque are done in the same way as mentioned above. The images with plaques are marked PLAQUE CCA FW and PLAQUE CCA NW, video recording is performed of both the live sequence and the frozen, marked images. R-wave triggered CCA IMT-registrations are recorded and the 3 optimal images are chosen from the cine-loop as described in paragraph 10. It is important to get representative images also from the near wall since IMT-measurements from the CCA-NW will be done off-line. The arrow-marker is placed in the same position as for the BULB measurements. The target site for IMT measurements of CCA is the 1 cm area from the start of the BULB and 1 cm downstream, proximally. The three images chosen to be recorded are marked CCA1, CCA2 and CCA3. If no measurable image is possible to obtain, an image from the CCA is still recorded and marked MC ("missing CCA"). All measurements on the far wall refer to the so-called "leading edge" principle (or "upper demarcation line"). These structures are not being different in thickness when the emitted power (mW/cm^2) or of the ultrasound instrument's gain setting are changed (nor are biological different conditions of subjects examined).

Near wall measurements, however, are performed on "far edge" principles, which means that IMT to some degree may be dependent on some of the technical conditions mentioned above (e.g., gain setting). Standardized examination conditions therefore are particularly important for the near wall measurements. It is, however, not possible, in technical terms, to obtain such ideal conditions because individually instrument adjusting alternatives always are more or less involved in processing optimal B-mode images. However, setting of functions such, as emitted power of ultrasound, preprocession, postprocession, gainsetting, etc. should be standardized as much as possible. Biologic inter-individual differences (obesity, position of the neck arteries, short or long necks, etc.) causing need of some different adjustments, however, are not possible to standardize. If the visibility of IMT and plaques is not optimal, the gainsetting (both the general and the segmental) should first be adjusted to improve the quality of the image. The gain should all the time be set high enough to identify soft, echolucent plaques but not too high to conceal small plaques due to "ultrasound noise". Only as an exception, adjustments of the other functions should be done.

12. **<u>Scoring of plaque-echogenicity</u>.** We aim at the highest echogenicity as possible since false too low echogenicity is a common problem due to several reasons: The plaque is cut too skew by the ultrasound beam, the longitudinal axis of the insonated vessel wall is not parallel to the ultrasound probe surface causing sub-optimal reflection of ultrasound energy (scattering), a far wall plaque is located within a ultrasound shadow from a calcified near wall plaque due to sub-optimal insonation angel. We therefore use the ultrasound signals from the media-adventitia interface as a reference of echogenicity to enhance precision on morphology scoring. This structure is easy to identify and is always presenting as high-echogenic, and is also localized close to the target, the atherosclerotic plaque.

    In a 4-step scale from 1 to 4, the media-adventitia echogenicity and plaques of similar echogenicity is given a value of 4. On a grey-scale, such objects appear white or close to white. A plaque of grade 1 consequently reflects no or almost no ultrasound signals and appears black or dark grey on images. Flowing blood appearing black on ultrasound images is the reference structure on this end of the scale. Grade 2 and 3 represent intermediary echogenicity: grade 1, the plaque consisting of more echolucent than echogenic material (≤ 50% echogenic material); grade 3, more echogenic than echolucent (> 50% echogenic material). Apart from the ultrasound reference structures used in this protocol, the echogenicity scoring is similar to previous reports in the literature.[1, 2]

    Grade 5 represents plaques that are not possible to classify on ultrasound of technical reasons (e.g., plaques in the far wall concealed by the echo shadow from calcified near wall plaques, not possible to angling of the probe to obtain representative images, plaque localized to high upstream to get high-quality images, etc.)

    When a plaque is heterogeneous and consists partly of high-echogenic and partly of low-echogenic material, the scoring of echogenicity is based of an overall impression of the dominating plaque echogenicity. When more than 80% of the plaque is of a given echogenicity, the echogenicity is scored as if the whole plaque consisted of this echogenicity although the rest of the plaque echogenicity was differing 2 or 3 grades from the dominating class of echogenicity. If the percentage is below 80%, interpolating is performed by judgement.

Thus, plaque echogenicity is classified as follows:

Grade 1: Echolucent (0- 20 % of plaque material is high-echogenic).
Grade 2: Predominant echolucent (21-50 % of plaque material is high-echogenic).
Grade 3: Predominant echogenic (51-79 % of plaque material is high-echogenic).
Grade 4: Echogenic (80-100 % of plaque material is high-echogenic).
Grade 5: Missing, not classifiable

In the same way, a total echogenicity status for an artery is determined if more than one plaque is present. The same limit of 80% is the basis of scoring of total plaque area.

AFTER EXAMINATION:

13. Do not remove the cassette from the video recorder before the end of the day, or when the cassette is full.

14. Check that the registration form is completed appropriately. In the ”Remarks” box, coding for reasons for missing of measurable images should be done:

    MB 1= missing images from BULB due to obesity.

    MB 2= missing images from BULB due to a steep angle between CCA and BULB.

    MB 3= missing images from BULB due to technically difficult examinations.

    MB 4= missing images from BULB due to previous surgery or radiation.

    MB 5= other reasons

    In the same way, missing coding for CCA and ICA is performed: MC 1, MC 2, etc.

A referral form to Department of Neurology, University Hospital, Tromsø is completed when a suspected carotid stenosis or occlusion are found. Two criteria for defining a stenosis are used. Either a velocity increase across an atherosclerotic plaque in BULB of 0.1 m/sec. or more or 0.2 m/sec. in ICA, compared to the reference velocity distally in ICA; or a plaque thickness that constitutes 35% or more of the lumen diameter at the plaque site. The velocities should be manually angle-corrected for the angle at which Doppler-beams are emitted into the vessel. Occlusion is suspected when the open lumen of the artery is not visible on B-mode or if there is a visible occluding plaque in the artery, and there is no detectable flow in the artery by pulsed Doppler or by colour-Doppler. The referral threshold should be low to avoid false negative stenosis cases. The person, who is referred, should be given a written and verbal information of the finding and clinical implications before living the room.

References:

1: Geroulakos G. et al. *Br J Surg.* 1993;80:1274-1277
2: Steffen CM. et al. *Aust. NZ J Surg.* 1989;59:529-534

English version June 2005 Stein Harald Johnsen

”Grabbing”-protocol

(Digitizing plaque images from SVHS-cassette)

- PC + monitor, and Panasonic 7560 video recorder + monitor are switched on. The video screen is preset to PAL.

- The videocassette is inserted in the video recorder. Wind on to the plaque image of interest. Check continuously the plaque registration form (Excel-sheet) to ensure that no plaque images are missed. The frame on the video screen should be smoothly adjusted until it is stationary, without any “snow”.

- Start **Matrox Intellicam** on the PC desktop.

- If this is the ***first ‘grab’*** from the videocassette, the GSM-value for the background colour of the recorded image should be calibrated according to the following procedure (1-5). If not, proceed to the next step.

    1. Grab an image (see the procedure for GRAB!).
    2. Save the image in the catalogue C:\My documents\Plaque\Test as test.tif.
    3. Export the image to Adobe Photoshop 3.0.
    4. Press the Image **m**ode – **G**reyscale, and then ’**OK**’ on the mini-menu ’Discard colour information?’
    5. Delimit a ’black’ area outside the B-mode picture on the screen with the squared tool function, and press **I**mage – **H**istogram. The mean value should be between 1-3. If it is <1 or >3, the ’BLACK LEVEL’-button on the Panasonic 7650’s ’TBC CONTROL’ is turned a little clockwise/counter-clockwise respectively, and the procedure is repeated until the mean value is between 1-3 (but not 0, then the ’BLACK LEVEL’ is too low!). This procedure should be repeated at every start-up, and each time a new videocassette is inserted, to ensure that background-black really *is* black.

GRAB!

- Press **Ctrl + M**, or press the **camera-icon** in the menu (nr 6 from left) to grab the image. Repeat until you have an optimal image. Every time Matrox Intellicam is started, the ‘Digitizer Configuration Format’ menu will appear on the screen – Choose ’PAL’ in the box and press ‘OK’.

- Save the image by pressing **Alt+F – A**, or **F**ile – Save **A**s, (but ***not*** **Ctrl+S**, or **Alt+F – S**, then the previous image will be erased!) and use the file name from the plaque registration form. *PS – check for writing error.* The file is saved in the catalogue corresponding to the tape number (Tape 01 etc…) under Tr4 or Tr5 respectively. (To simplify the file name routine, the file can be copied from Excel, and pasted in the file name column in Intellicam, and thereafter press <Enter> to save…but still check for writing error!!). Fill in ’grab’ – date (format: ddmmyy, f. ex 011102, 150103) on the Excel sheet as a ‘receipt’.

- Wind on to the next plaque recording, adjust smoothly and repeat the procedure…11000 times!

Appendix F

Digit-symbol coding test
Cognitive testing
Tromsø 5 and 6

Digit -symbol coding test

1	2	3	4	5	6	7	8	9
–	⊥	⊐	└	⊔	○	∧	X	=

ØVING

2	1	3	7	2	4	8

2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4	1	5	4	2	7	6

3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3	6	2	5	1	9

2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1

7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6	3	6	4

Hvis oppgaven ikke er utført, angi hvorfor:

Trøtt . . . . . ☐ Vegrer seg . . . . . ☐ Praktiske hindringer . . . . . ☐ Afasi . . . ☐

Ser for dårlig . . ☐ Hører for dårlig . . ☐ Utilstrekkelig håndmotorikk . . . ☐

Annet (angi hva) _____

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