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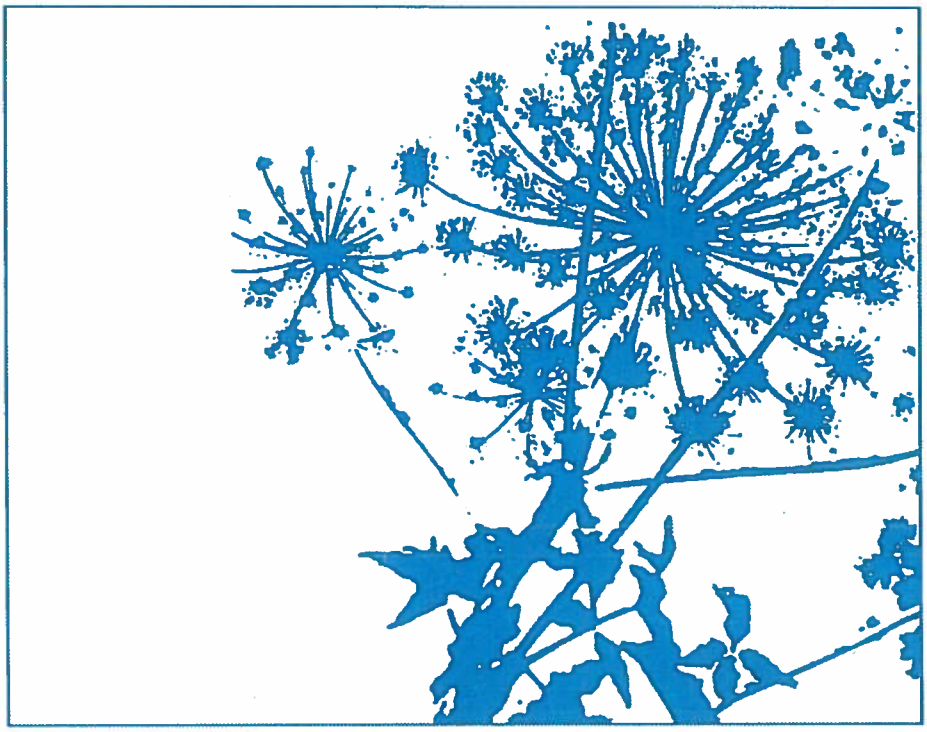

THE STENOTIC CAROTID ARTERY PLAQUE. PREVALENCE, RISK FACTORS AND RELATIONS TO CLINICAL DISEASE

THE TROMSØ STUDY

Ellisiv B. Mathiesen

Tromsø 2001

Institute of Community Medicine
University of Tromsø

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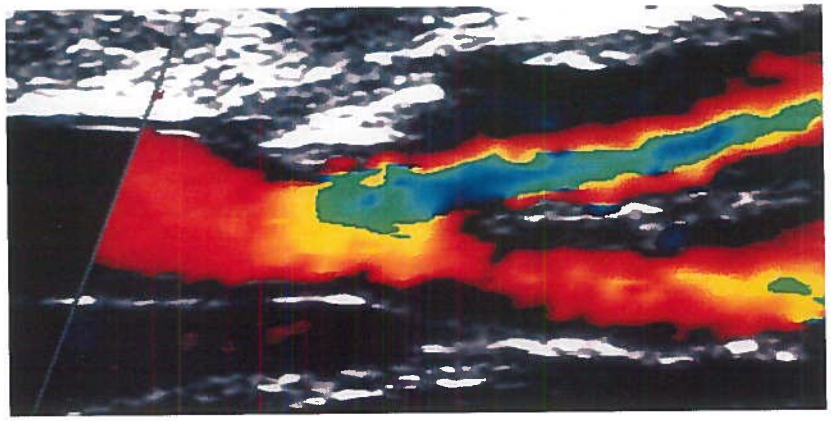

by

Ellisiv B. Mathiesen

Institute of Community Medicine
University of Tromsø, Norway

Tromsø, 2001

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List of papers

This thesis is based on the following papers:

I. Intersonographer reproducibility and intermethod variability of ultrasound measurements of carotid artery stenosis. The Tromsø Study
Cerebrovasc Dis 2000;10:207-213

II. Prevalence of and risk factors associated with carotid artery stenosis. The Tromsø Study
Cerebrovasc Dis 2001;12:44-50

III. Low levels of high-density lipoprotein cholesterol are associated with echolucent carotid artery plaques. The Tromsø Study
Stroke 2001. In press

IV. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis. The Tromsø Study
Circulation 2001;103:2171-2175

The papers will be referred to by their Roman numerals in the text.

1. Introduction

Stroke is the second leading cause of death in the world and is responsible for a high percentage of major disability,[1] requiring substantial resources spent on care and rehabilitation. Atherosclerosis due to lipid accumulation in the vessel wall with formation of stenotic atheromatous plaques in the carotid bifurcation and/or the internal carotid artery is an important cause of stroke. In 1991, two large, multi-center trials reported that carotid endarterectomy was of benefit to patients with a degree of stenosis above 70%, and thus showed that the degree of stenosis was a major risk factor for ipsilateral stroke.[2; 3] However, it is well known that many high-grade stenoses remain stable and never cause cerebrovascular events, while others develop rapidly and produce serious, potentially life-threatening disease. While the majority of patients presenting with transient ischemic attack (TIA) and stroke has an ipsilateral carotid lesion, only about half of them have a hemodynamically significant carotid stenosis.[4; 5] Only 5-15% of strokes are heralded by a TIA.[6] This has led to a search for additional risk factors which might help identify the individuals with a high risk for stroke.

Several studies have showed that the coronary plaques which are most vulnerable to rupture and thereby cause clinical disease, are those with an atheromatous, lipid-rich core covered by a thin, fibrous cap.[7; 8] The rupture of the fibrous cap results in exposure of thrombogenic plaque constituents to the bloodstream, resulting in thrombosis, and this mechanism is generally believed to be the event leading to clinical incidents in coronary heart disease. In a study on carotid endarterectomy specimens, Carr et al. found that plaque rupture, fibrous cap thinning and fibrous cap foam-cell infiltration were significantly more frequent in symptomatic than in asymptomatic plaques,[9] indicating that the same process is the critical event also in carotid disease. Both pathology and ultrasound studies have found that plaque morphology in the carotid arteries is associated with clinical events.[10]

The carotid arteries are readily accessible to ultrasound imaging, and this makes it possible to evaluate plaque morphology characteristics non-invasively. Ultrasonographic evaluation of the carotid arteries is a safe, low-cost method for the assessment of atherosclerosis, and suitable for population-based studies.[11] It is based on two principles: high-resolution B-mode imaging to directly visualize the arterial wall and any local disease, and Doppler flow studies to provide physiologic information on disturbances of blood flow velocity associated with stenosis or

absence of flow to suggest occlusion. This combination of imaging and Doppler flow analyses permits simultaneous evaluation of vascular morphology and hemodynamics.

1.1. Basic principles of ultrasound assessment of carotid arteries

B-mode

When ultrasound waves are transmitted into the tissue, parts of the ultrasound will be absorbed by the tissue and parts of it are reflected. The ultrasound transducer contains an oscillating piezoelectric element which sends pulses of ultrasonic waves into the tissue. The transducer is also able to receive reflected ultrasound in a certain period after the transmission of waves. This reflectance or backscatter of acoustic energy – the echo – is converted to electrical signals, which are processed into a two-dimentional grey-scale image by a computer. The amount of reflected energy is dependent on the differences in acoustic impedance between tissues. Acoustic impedance is defined as the product of material density and the speed of sound. The higher the differences in density are between the tissue layers, the more energy is reflected, and the brighter will the insonated object appear on the B-mode image (B; brightness). Fibrous and calcified tissue will appear bright, whereas moving blood cells will appear black.

Doppler

As an atherosclerotic plaque progressively narrows the lumen of a vessel, the velocity of the flow at that site must increase if constant flow is to be maintained.[12] This basic principle is used to calculate the degree of stenosis by Doppler ultrasound techniques. Ultrasound backscattered from particles in the flowing blood, mainly red blood cells, is shifted in frequency by an amount proportional to the velocity of these particles. This shift in the frequency of transmitted ultrasound waves is called the Doppler signal and is used to calculate the velocity of flowing blood. The relationship is expressed in the Doppler equation:

$$CFd = 2VFo \cos \theta$$

where Fd = the Doppler shifted signal, V = velocity of the red blood cells within the Doppler sample, C = constant related to the speed of sound in tissue (15.4×10^6 cm/sec), Fo = frequency of the incident Doppler beam (5×10^6 Hz) and θ = Doppler angle between the incident beam and the axis of flow. In the Duplex machine, θ can be calculated from the B-mode image and Fd can be measured by the use of a spectrum analyzer which permits quantification of the frequencies of the reflected Doppler signal. This allows instantaneous calculation of the velocity of flow at any time during the cardiac cycle.[12] As flow velocity is proportional to the cross-sectional area of the arterial lumen at

the site of measurement, this information can be used to deduce the degree of luminal narrowing.

The addition of color-flow technology to duplex scanning allows visualization of blood flow within the vessel. Velocity information is converted and mapped as color and superimposed on the grey-scale ultrasound image. Color-Doppler makes it easy to interrogate vascular structures and show the pattern of blood flow within. It also produces better outlines of the vessel wall, and can thereby add valuable information on vessel wall abnormalities.

1.2 Validity and reproducibility of ultrasound assessments of carotid stenosis

The validity of ultrasonography has been examined in numerous studies[12-19] In most studies intraarterial angiography is used as the gold standard, less often comparisons are made against pathology studies of endarterectomy specimen.[14; 17-19] The conclusion of virtually all of these studies is that the correlation between ultrasound and both angiography and pathology studies is good. Nevertheless, controversy exists about the value of ultrasonography;[20-22] some authors recommend the use of ultrasound only as a screening device for the exclusion of patients with no artery disease,[20] whereas others have found ultrasound more accurate than angiography in predicting the degree of stenosis.[17; 19; 23; 24] When carotid endarterectomy was reported to be of benefit in symptomatic patients with a degree of stenosis above 70%[2; 3] and in asymptomatic patients with stenosis above 60%,[25] this spurred new interest in how carotid stenosis should be diagnosed and measured.[26] Many studies have been conducted to define the duplex criteria that most accurately predict stenosis at or above the defined cutoff-points.[24; 27-32] However, to date, there is no consensus on how the presence and the degree of carotid stenosis most reliably are estimated, neither by conventional intraarterial angiography or by the various ultrasound techniques available.

The reproducibility of ultrasound assessment of carotid stenosis has not been studied extensively. Sources of error in ultrasound-assessment of carotid disease fall into four broad categories: 1) factors intrinsic to the region being studied, such as size and depth, 2) variations attributable to the equipment, such as transducer beam pattern and frequency spectrum, 3) factors related to the examination technique, such as angle of interrogation, sample volume size and placement, and angle correction, and 4) interpretation of the ultrasound images obtained (reader variability). Important variability related to equipment has been found in previous studies.[15; 33-35] Studies on factors related to examination technique and interpretation, the intra- and

inter-observer variability, have shown results that are difficult to interpret and partly contradictory.[35-43]

How we define and measure the degree of stenosis is not only important for selection of patients to surgery, but will also affect the estimated prevalence of carotid artery stenosis. In principle, any degree of lumen narrowing can be defined as stenosis. Previous population-based studies on the prevalence of carotid stenosis have been based on ultrasound screening, but the methods and cutoff points which have been used have varied. Prevalence of carotid stenosis has not been measured previously in Norway.

1.3 Classification of ultrasound-assessed plaque morphology

Ultrasonography allows characterization of carotid plaques according to how they appear on the B-mode image. Different classifications based on echogenicity, defined as reflectance of the emitted ultrasound signal, are used in the literature. Johnson et al. used the categories soft, dense, and calcified.[44] Others have also used three categories, referred to as hypoechoic or echolucent, intermediate or isoechoic, and hyperechoic or echorich.[45-47] The classification proposed by Gray-Weale at al. in 1988[48] describes four categories of plaque echogenicity; echolucent, predominantly echolucent, predominantly echogenic and echogenic. Others have used the terms heterogenous/homogenous, where heterogenous is used to describe plaques with mixed high-, medium-, and low-level echoes, and homogenous refers to plaques with uniformly high- or medium-level echoes.[49-52] Still others use the term homogenous to describe a plaque with uniform echo-structure, independently of the amount of echo (i.e., both an echolucent and an echogenic plaque can be described as homogenous), while heterogenous is used to describe a plaque with areas of mixed echogenicity.[45; 53; 54]

1.4 Validity and reproducibility of ultrasound-assessed plaque morphology

Plaque morphology as assessed by ultrasound has been validated against histology in several previous studies.[29; 45; 47-49; 51; 55-59] Wolverson et al. first showed that lipid aggregates appeared echolucent on B-mode images, while areas of fibrosis and calcified regions appeared highly echogenic, the latter with acoustic shadowing.[55] Later, several quantitative studies of plaque constituents have confirmed these results.[45; 47; 56; 57]

Much controversy exists in the literature about the relationship between intraplaque hemorrhage and ultrasound-assessed plaque echogenicity and structure, and also on the clinical relevance of intraplaque hemorrhage. In 1979, Imparato et al. reported that hemorrhage was frequent in plaques associated with focal

neurological symptoms,[60] and several others have reported similar results.[49; 61; 62] This led to increased interest in the ability of ultrasound to detect intraplaque hemorrhage. Many early reports on ultrasound-assessed plaque morphology reported a high percentage of intraplaque hemorrhage in plaques that were described as echolucent or, more often, as heterogenous (mixed echolucent, intermediate, and echogenic and/or calcified areas),[48; 49; 51; 54; 56] and in some of these studies, the intraplaque hemorrhage was associated with the presence of symptoms.[49; 56] However, in many of these studies only the presence of hemorrhage, and not the relative volume of hemorrhage was registered. Quantitative assessments of plaque constituents have shown that hemorrhage, when present, usually occupies only a small amount (1-2%) of the total plaque volume,[45;47;57;63-65] making it unlikely that such small volumes can be reliably detected by ultrasound. In addition, several later studies failed to find any correlation between the presence of intraplaque hemorrhage and symptoms.[9; 57-59;65;66] Widder et al. concluded that the lacking ability of ultrasound to distinguish between hemorrhage and lipid deposits was unimportant since both plaque constituents were closely correlated to ipsilateral neurological symptoms.[54] Grønholdt et al. reported a clear association between lipid-deposits and hemorrhage in plaques, interpreted as a support to the theory that lipid-rich plaques are more prone to rupture.[47]

Thrombi are thought to be a result of plaque disruption with subsequent exposure of the atheromatous lipid-rich core to the bloodstream. Fresh thrombi will appear as echolucent structures on B-mode ultrasound, often only possible to recognize with the additional use of color-Doppler.[67] While a large thrombus can be distinguished from an echolucent plaque by the absence of a lumen-lesion interface,[58] smaller thrombi may not be distinguished from an echolucent plaque.

Most authors have found the reproducibility of plaque morphology assessments to be acceptable,[46;53;68-71] although there are indications that reproducibility may be reduced in high-grade stenosis.[72] Some studies have obtained higher reproducibility when classifying plaque morphology in two categories instead of four.[53; 71]

1.5 Risk factors for ultrasound-assessed plaque morphology

Few studies have examined risk factors associated with ultrasound-assessed plaque morphology. Grønholdt et al. found in a study of 85 symptomatic patients with carotid stenosis that echolucent plaques were associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins and younger age.[70] In a later

study with computerized assessment of plaque echogenicity, they found that triglyceride-rich lipoproteins were predictors of echolucent plaques, and that both fasting and postprandial HDL cholesterol levels were inversely associated with the total plaque volume, total plaque lipid and total plaque fibrous tissue in endarterectomy specimens.[73] In the European Carotid Plaque Study, males had significantly more soft tissue in plaques than females, while plaques from patients with arterial hypertension had less soft tissue than normotensive patients.[45] In the Atherosclerosis Risk in Communities (ARIC) Study, smoking and hypertension was associated with plaques with acoustic shadowing (as opposed to plaques without acoustic shadowing).[74]

1.6 Ultrasound-assessed carotid artery plaque morphology as a risk factor for stroke

In 1985, Johnson et al. reported that echolucent plaques were associated with a higher risk for stroke.[44] Later, several studies have supported the notion that carotid plaque morphology may be associated with clinical cerebrovascular ischemic events.[46; 50; 67; 69; 75-84] Most of these studies are small, with selected groups of patients, and few of them are longitudinal.[46; 50; 75; 79; 80] Only two of the prospective studies have made adjustments for other cerebrovascular risk factors.[46; 50]

As an association between the degree of stenosis and plaque morphology has been reported,[50; 75; 81; 85] it is especially important to adjust for the degree of stenosis. Furthermore, the natural history of plaque morphology can not be properly evaluated in selected groups of (usually) symptomatic patients seen in ultrasound laboratories/clinics. This can however be assessed within the setting of a population-based study. Only one previous population-based study on plaque morphology has been published.[46]

2. Aims of the thesis

The aims of the thesis were as follows:

- To assess the interobserver reproducibility of measurements of carotid stenosis within the setting of a population study, and to compare three different ultrasound methods by which stenosis can be measured.
- To estimate the prevalence of carotid stenosis in a general population, and to study risk factors for carotid stenosis.
- To assess risk factors associated with plaque morphology in stenotic arteries.
- To assess whether plaque morphology is a predictor of clinical cerebro-vascular events (stroke, transient ischemic attack, amaurosis fugax).

3. Study population and methods

3.1. The Tromsø Study

The Tromsø Study is a single center prospective follow-up study of the population in the municipality of Tromsø, Norway, conducted by the Institute of Community Medicine at the University of Tromsø, in co-operation with the National Health Screening Service and the Community Health Services in Tromsø. The study design includes repeated population health surveys to which total birth cohorts and random samples are invited. The main objective of the study is to investigate determinants and distribution of cardiovascular disease. Four surveys have so far been carried out, the first in 1974, followed by the next in 1979-80, in 1986-87 and in 1994-95.

At the 1994-95 survey, all eligible persons were contacted by an invitation letter with a one-page questionnaire on the reverse side. Information on the following main topics were obtained by the questionnaire: coronary heart disease, previous stroke, hypertension, diabetes mellitus, physical activity during leisure time, dietary habits, smoking habits, working situation, and family history of cardiovascular disease. The invitation leaflet, the questionnaire and the declarations of consent are presented in Appendix A.

The questionnaires were returned when attending the survey, where standardized measurements of blood pressure, weight, height and nonfasting serum lipids were made. The participants were then handed a stamped and addressed envelope containing a second questionnaire, which they were asked to fill in at home and return by mail. The following topics were covered in the second questionnaire: previous and present dietary habits, alcohol intake, use of drugs, previous and/or present illnesses (other than those reported in the first questionnaire), illnesses among close relatives, life style factors, social conditions, education, use of health services, and, for women only, menstruation and pregnancies. A somewhat shorter questionnaire was used for participants aged 70 years and above. The second questionnaires are presented in Appendix B. An overview of all standardized measurements at the first and the second visit is given in Appendix C.

The survey consisted of two screening visits 4 to 12 weeks apart (Figure 1). All men and women older then 24 years (born before 1970) and who in 1994 were registered as residents of Tromsø, were invited to the first visit. The total number invited was 35 443, and 27 168 (76.7%) attended the first visit. To the second visit, all subjects aged 55-74 years and random 5% samples in the other 5-year birth cohorts were invited. The second visit also

cohorts were invited. The second visit also included a selected group of 308 men aged 40-54 years, who in the 1979-80 survey had taken part in a family intervention trial (FIV), where the selection criteria were total cholesterol values in the highest decile and/or relative high density lipoprotein (HDL) cholesterol in the lowest quintile.[86] Thus, the total number invited to the second visit was 8732 subjects of whom 6889 (78.9%) attended (Table 1). Ultrasound examination of the right carotid artery were performed on 6727 of those who attended the second visit, 76.9% of the eligible population (Figure 1). Among these, ultrasonography of both carotid arteries were performed on 784 persons. Table 1 shows the age- and sex-specific attendance rates to both visits.

All persons diagnosed with carotid stenosis were asked to participate in a follow-up study (Figure 1). They were also offered referral to the Department of Neurology at the University Hospital of Tromsø for clinical neurological follow-up. The time available for each examination at the screening visit was rather limited (15 min), which sometimes could make it hard to reach a conclusion. Thus, the sonographers were instructed also to refer cases where scanning was difficult or when

Figure 1. Outline of present study

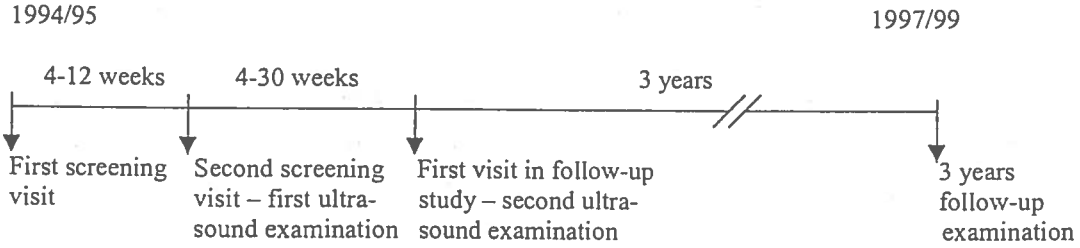


Table 1. Response rate (%) to the second visit of the fourth survey of the Tromsø Study

Age (yrs)	Men	Women	All
25-29	42.6	55.1	48.3
30-34	55.0	65.1	60.3
35-39	59.8	61.9	61.0
40-44	62.8	79.8	72.1
45-49	79.6	84.3	81.0
50-54	76.8	95.2	81.4
55-59	77.5	86.5	81.8
60-64	81.4	85.8	83.6
65-69	82.5	83.8	82.9
70-74	77.8	78.1	78.0
75-79	71.3	66.8	68.8
80-84	47.1	44.4	45.3
85+	33.3	66.7	50.0
Total	76.9	80.9	78.9

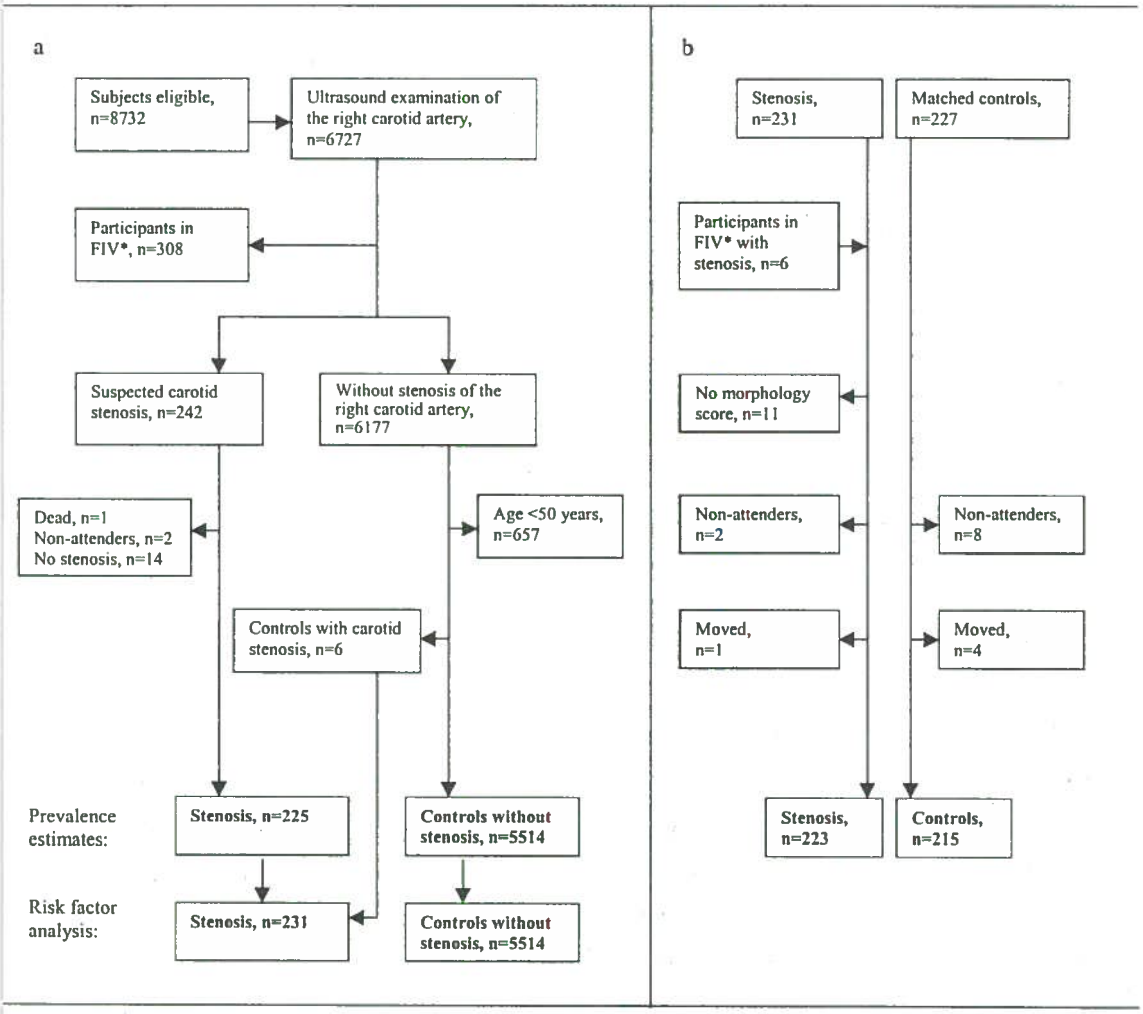
they were in doubt about whether the criteria for stenosis were fulfilled or not, e.g. when calcified near wall plaques caused acoustic shadowing of the vessel lumen. The intention was to achieve a high degree of sensitivity, be it at the expense of a moderate or low specificity. A total of 248 persons with suspected stenosis (6 with left-sided and 236 with right-sided or bilateral stenosis) were asked to participate In the follow-up study. Two persons with stenosis declined to participate, 1 died shortly after screening, and 14 were found to not fulfil the criteria for stenosis/occlusion when they were reexamined at the second ultrasound examination, and were excluded.

A group of 232 persons without right-sided stenosis, matched by age and sex, but otherwise randomly selected, were also asked to participate in the follow-up study. At the second ultrasound examination, 4 of these 232 persons were found to have stenosis of the left carotid artery, whereas 1 had stenosis and 1 had occlusion of the right carotid artery. These 6 persons are excluded in the calculation of stenosis prevalence, but are otherwise included among the subjects with stenosis.

Flow charts of the participants in the various parts of the study are shown in Figure 2.

In paper I, the number of participants is correctly given as 6727 persons (Figure 2). The response rate of 88% was, however, incorrect. This was due to errors in the data file of invited people.

Figure 2. Flow-chart of participants in the study. a: Stenosis prevalence and risk factors (paper II). b: The follow-up study (paper IV)



*FIV = family intervention trial

In paper II and paper III, the 308 high-risk men who previously were participants in the family intervention trial,[86] six of them with stenosis of the right carotid artery, were excluded (Figure 2). This was done in order to present results on prevalence from an unselected general population. In paper II, the reference population was all survey participants above the age of 50 years without known stenosis of the carotid arteries (n=5514). The cutoff was set at age 50 in order to assure approximately the same range of age among cases and other study participants. For a few variables, however, only data on the participants in the follow-up study were available.

In paper III and IV, we have used a smaller reference population (controls) than in paper II. Since data on clinical end-points were available only for the participants of the follow-up study, only these subjects were included in paper IV (Figure 2). We chose the same reference population in paper III as in paper IV in order to describe baseline characteristics of the participants in the follow-up study. In paper IV we included all subjects with carotid stenosis and all matched controls, regardless of whether they were previous participants of the intervention trial. This was justified by the aim of and the prospective nature of the follow-up study, which was to assess whether plaque morphology predicts ischemic cerebrovascular events, with appropriate adjustments for the baseline levels of total cholesterol and HDL cholesterol, and other risk factors.

3.2. Ultrasound examinations of the carotid artery.

The protocol for the ultrasound screening procedures (Appendix D) were partly based on the standardized imaging techniques used at the Wallenberg Laboratory for Cardiovascular Research at Gothenburg University, Sweden and in the Rotterdam Study.[87;88] Three sonographers (a neurologist, a physician and a technician) performed the ultrasound examinations at the screening, after completing a 2-month training program to ensure standardized measurements. The intra- and interobserver reproducibility on measurements of intima-media thickness (IMT), plaque occurrence, plaque thickness, and plaque morphology was good.[53; 89]

The ultrasound measurements are described in detail in the papers, especially in paper I. Stenosis was considered to be present when one or both of the following criteria were present: 1) Peak systolic velocity in tightest stenotic part (PSVs) ≥ 0.2 m/sec higher than peak systolic velocity at the point of reference (PSVr), or ≥ 0.1 m/sec if the stenosis was located

to the bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery (with parallel walls) was used as the point of reference. 2) Thirty-five % or more reduction in lumen diameter on a longitudinal B-mode scan.

Both the right and the left carotid arteries were examined at the second ultrasound examination. The original and residual lumen in both longitudinal and cross-sectional planes were measured. With the use of color-Doppler, peak systolic velocities in and distal to the stenosis were measured. The degree of stenosis was then calculated by the following equations: 1) Lumen diameter reduction method: (plaque thickness/lumen diameter) x 100 %, 2) Cross-sectional lumen area reduction method: (plaque area/lumen area) x 100%, 3) Peak systolic velocity ratio method: (1–PSVr/PSVs) x 100 % (Figure 3). These three methods are referred to as the diameter method, the area method, and the velocity method (paper I and II).

Occlusion was diagnosed when an open lumen of the artery was not visible on B-mode or if there was a visible occluding plaque in the artery, and there was no detectable flow in the artery by pulsed Doppler or by color-Doppler.

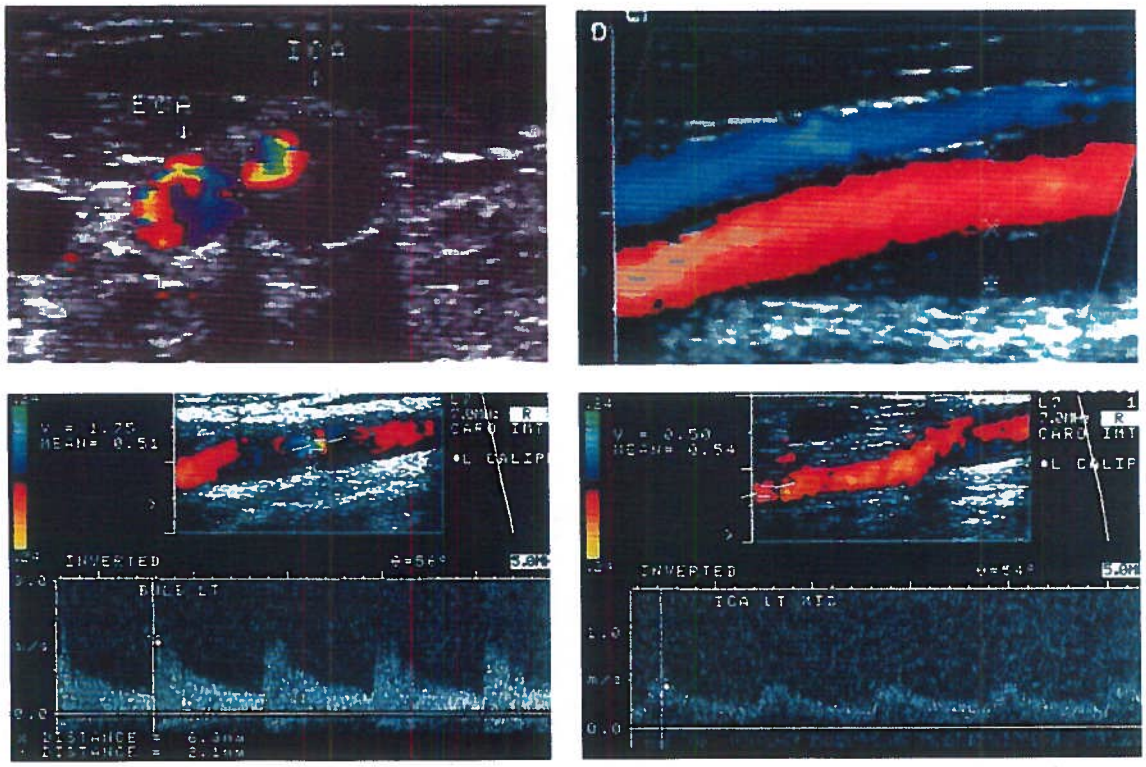
Plaque morphology in terms of echogenicity, defined as reflectance of the emitted ultrasound signal, was assessed in a modified version of the classification proposed by Gray-Weale et al,[48; 53] and graded from 1 to 4 as echolucent, predominantly echolucent, predominantly echogenic or echogenic. The vessel lumen was used as the reference structure for defining echolucency, and the bright echo-zone produced by the media-adventitia interface in the far wall was used as the reference structure for defining echogenicity. Plaque morphology was also classified according to structural appearance criteria as either heterogenous or homogenous. Plaques were classified as heterogenous if the echogenicity of more than 20% of the plaque area differed from the echogenicity of the rest of the plaque by two or more echogenicity grades. All other plaques were defined as homogenous.[53]

In the case of bilateral stenosis, the carotid artery with the highest degree of stenosis was selected for analysis.

3.3 Follow-up

The selection of subjects for the follow-up study is described above. Three years after the screening, all subjects with stenosis and all control subjects who took part in the first examination of the follow-up study (i.e., the second ultrasound examination), were invited to a new examination which included a structured interview about medical history, standardized

Figure 3. B-mode and color-Doppler images of carotid stenosis



Top panel, left. Stenosis of the internal carotid artery (ICA) caused by an echolucent plaque, shown in cross-sectional plane. The dotted line marks the original lumen (and enables calculation of original lumen area in mm^2), while the residual lumen is filled with color.

Top panel, right. Stenosis in the carotid bulb shown in the longitudinal plane. One pair of calipers (x) marks the plaque thickness, the other (+) the lumen diameter.

Bottom panel, left. Color-Doppler measurement of peak systolic velocity in carotid stenosis (PSVs). The cursor is placed in the carotid bulb. The PSVs of 1.75 m/sec is given in the upper left corner of the picture.

Bottom panel, right. Color-Doppler measurement of peak systolic velocity (PSVr) in the same artery, with the cursor placed distally in the internal carotid artery. The PSVr of 0.50 m/sec is given in the upper left corner of the picture.

measurements of blood pressure, weight, height, clinical neurological examination, ultrasound examination and blood tests. All tests except the blood tests were performed by the same examiner, who was blinded to previous assessments of plaque morphology, but not to whether the participants were previously diagnosed with stenosis or not.

4. Main results

4.1 Reproducibility (paper I)

The mean degree of stenosis and the median absolute between observer difference of the degree of stenosis by the velocity method were 46.3% and 10.8%, respectively. The corresponding values were 51.0% and 5.8% for the diameter method, and 57.1% and 7.2% for the cross-sectional lumen method. The limits of agreement for intersonographer reproducibility varied between ±19.7% and ±26.5%. For all methods, reproducibility was better with increasing degree of stenosis. Differences between the methods were large in low-grade stenosis, but were acceptable in high-grade stenosis. Agreement on plaque echogenicity and heterogeneity was assessed by use of the kappa (κ) statistic and was moderate (κ=0.56 and κ=0.60, respectively). Considerable differences in ultrasound measurement of stenosis, which could lead to different clinical conclusions, were encountered by the use of all three ultrasound methods.

4.2 Prevalence of and risk factors for stenosis (paper II)

The overall prevalence of stenosis in the right carotid artery was higher in men (3.8%, 95% confidence interval [CI] 3.2-4.6%) than in women (2.7%, 95% CI 2.2-3.3%) (p=0.001). The prevalence gradually increased by age in both genders. No men below the age of 50 and no women below 55 years had carotid stenosis. Age, male gender, current smoking, total cholesterol, HDL cholesterol (inverse), fibrinogen, and systolic blood pressure were independent predictors of carotid artery stenosis in both women and men. Carotid stenosis was also associated with coronary heart disease and peripheral artery disease.

4.3 Risk factors for plaque morphology (paper III)

The main finding in this paper was the inverse relationship between HDL cholesterol and plaque echolucency. For one standard deviation increase in HDL cholesterol, the adjusted odds of having a more echolucent plaque decreased by about 30% (odds ratio [OR] 0.69, 95% CI 0.52-0.93). In addition, increasing degree of stenosis was independently associated with increased risk of having an echolucent

plaque. Systolic blood pressure was also associated with low echogenicity, however, this finding could not be reproduced when using results from plaque morphology assessments made at the screening visit.

4.4 Plaque echogenicity and risk of ischemic cerebrovascular events (paper IV)

In the follow-up period (median 3.0 yrs), 44 subjects experienced one or more ischemic cerebrovascular events. Plaque echogenicity, degree of stenosis, and white blood cell count were independent predictors of cerebrovascular events. The unadjusted relative risk for cerebrovascular events was 13.0 in subjects with echolucent plaques (95% CI 4.5-37.4), and 3.7 (95% CI 0.7-18.2) in subjects with echogenic plaques when subjects without stenosis were used as the reference. When adjustments were made for age, sex, degree of stenosis and cardiovascular risk factors, the relative risk for cerebrovascular events in subjects with echolucent plaques was 4.6 (95% CI 1.1-18.9), and there was a significant linear trend for higher risk with increasing plaque echolucency. The relative risk for a 10% increase in the degree of stenosis was 1.2 (95% CI 1.04-1.4). In conclusion, subjects with echolucent, lipid-rich atherosclerotic plaques have increased risk of ischemic cerebrovascular events independent of degree of stenosis and cardiovascular risk factors. Subjects with high risk for ischemic vascular events may be identified by ultrasound assessment of plaque morphology.

5. General discussion

5.1. Methodological considerations

5.1.1 Internal validity

The internal validity (or lack of systematic error) of a study refers to whether the results obtained are representative or true for the population under study.[90] Three general types of biases may threaten the internal validity of an epidemiological study; selection bias, information bias and confounding. Any observed association may also occur by chance alone.

Selection bias – cross-sectional study

Distortions that result from procedures used to select subjects and from factors that influence study participation are called selection bias.[90] Although the overall response rate in the cross-sectional study was high, the age-specific attendance rates were low in the younger age-groups (women < 40 years and men < 45), and for both sexes aged 80 and above (Table 1). We have no direct information on the non-responders in the 1994/95 survey, however, a comparison between attenders

and non-attenders at the second visit of some variables assessed at the first visit, shows that blood pressure, serum lipids and body mass index were similar among attenders and non-attenders, while a larger proportion of non-attenders than attenders were smokers.[91] Similar results were found in a previous survey of the Tromsø Study.[92] However, subjects who participated at the first visit, but failed to attend to the second visit, are different from non-responders to both visits since they have demonstrated their interest by attending the first visit. Several studies have found trends towards higher levels of cardiovascular disease among non-attenders than among attenders.[93; 94] This may be an important source of bias especially in the elderly, who may not attend because they are sick or disabled. In the present study, selective non-attendance of subjects with higher levels of cardiovascular risk factors could lead to underestimation of both the prevalence of stenosis and of the true relationship between risk factors and stenosis. Selective survival especially among the elderly might be another source of bias, resulting in a high representation of participants with low levels of or different response to risk factors compared to deceased persons from the same birth cohorts.

It is likely that the prevalence of stenosis is underestimated in the older age groups in the present study (paper II). It is less likely that the relationship between risk factors and presence of stenosis/plaque morphology is biased since this would occur only if the relationship is different among attenders and non-attenders.

Selection bias – follow-up study

Selection bias is usually not a problem in prospective cohort studies since information on exposure is ascertained before the development of the outcome(s) of interest. However, if the follow-up rate in a prospective study is lower than 95%, selection bias should be considered.[95] In the present study (paper IV), the non-attendance rates at the three years follow-up examination were 1.3% and 5.4% among subjects with and without stenosis, respectively (χ^2 5.94, p=0.015). When those who are lost to follow-up differ from those who are not with respect to both the exposure and the outcome variable, this can bias the estimates of the association.[96] No medical follow-up information was available for those persons who had moved out of the town (n=5), but since this proportion was very low, it is unlikely to have biased the estimates. For those who did not respond to the invitation (n=10), hospital records were available for all. The non-participants were significantly older, had lower total cholesterol levels, were more likely to be women and were more

likely to have coronary heart disease than participants. There were no differences in the frequency of malignant disease, hypertension, smoking, peripheral artery disease, stroke, or diabetes between participants and non-participants (unpublished data). One subject without stenosis had been hospitalized due to an episode classified as transient ischemic attack (TIA) (left sided paresis of duration shorter than 24 hours and a normal CT scan of the brain), otherwise there were no reports of cerebrovascular events. Inclusion of these subjects in the survival analysis did not change the results reported in paper IV. In conclusion, we think selection bias in the follow-up study is negligible.

Information bias – cross-sectional study

Information bias may occur if there are systematic differences in the way data on risk factors/exposure or endpoints/ outcome are obtained between study-groups. Most errors related to ultrasound examination can be expected to be random, non-differential. The interobserver variability on classification of plaque echogenicity (paper I) indicates that some misclassification occurred, thus it is possible that some stenoses were erroneously classified as non-stenotic. The chance of diagnosing a non-stenotic artery as stenotic was lower since all subjects with suspected stenosis of the carotid arteries were examined twice.

Obesity is a factor which could lead to misclassification. Ultrasound penetrates fatty tissue well, but since the length the ultrasound can penetrate is limited, obesity will lead to relatively deeper localization of the carotid arteries in the neck, and thus make the imaging conditions less favorable. Such measurement bias would weaken the true relationship between body mass index and stenosis/plaque morphology.

The questionnaire instrument is subjective and imprecise. Self-reports on medical conditions that are well defined and relatively easy to diagnose often have a high positive predictive value (PPV).[97] This is the case for diabetes and myocardial infarction. Stroke is less clear-cut, however, in a recent report from the fourth survey of the Tromsø Study, the PPV of self-reported stroke was 0.79, the sensitivity 80% and the specificity 99%.[98] Very few of the subjects had previous knowledge about the status of their carotid arteries, and thus any misclassification of subjects is likely to be random with respect to the association of interest.

The diagnosis of transient ischemic attacks (TIA) made at baseline was based upon interviews made by the two neurologists. The diagnosis was defined as a new-onset focal neurological abnormality

lasting less then 24 hours with no other apparent cause than cerebrovascular, and is exclusively based on the patient's history.[99] It has previously been shown that the interobserver agreement for this diagnosis is good (κ=0.65).[100] We have not assessed the interobserver agreement in the present study.

The questions on smoking used in this study have been validated previously.[101] In the present papers, we chose to use data on current smoking, and not data on previous smoking habits (such as the amount of cigarettes smoked per day or the number of years with smoking), both because such data are more prone to recall bias and because the use of these variables did not add any information to the analysis.

Non-fasting blood lipids were used in the Tromsø Study. The effect of the non-fasting condition on total cholesterol and HDL cholesterol is negligible, but triglyceride levels vary considerably throughout the day.[102] This variability in triglyceride levels can partly be corrected for by adjusting for time since last meal, but since this did not affect the estimates in the present study we omitted it from the final analyses. Previous studies showed that non-fasting triglyceride concentration was an independent predictor for mortality from coronary heart disease, cardiovascular disease and any cause mortality among middle aged Norwegian women[103] and an independent predictor of myocardial infarction in male physicians.[104] Postprandial hyper-triglyceridemia has been found to be a better predictor of IMT than fasting levels.[105] Most of our lives are spent in the postprandial state, thus non-fasting triglycerides may better reflect the biologically relevant condition than fasting values.[106] It is also important to note that the non-fasting condition would not affect subjects with and without stenosis differently.

Participants who at the first visit of the survey had lipid or blood pressure levels above certain limits, were informed about this. It is possible that some of them received medical advice in the time between the first and the second visit (4-12 weeks) which may have altered their risk factor levels. Because of this, lipid and blood pressure measurements from the first visit were used in all analyses.

Information bias – follow-up study

In paper IV, bias due to different diagnostic procedures among those who were dead before the 3-year follow-up exam and those who took part in the follow-up exam might result in an underestimation of clinical events among the dead. This relates especially to TIAs, which may not be reported unless specifically asked for. Such mis-

classification of outcome would lead to either underestimation of the true relationship between risk factors and clinical events, or not influence the association. It has been shown that the agreement for vascular territory in patients diagnosed with TIA was poor (κ=0.31),[100] which is of importance when correlating symptoms of relevant vascular territories to stenosis. Furthermore, the fact that the observer was not blinded to whether a participant had stenosis or not, could lead to falsely diagnosing more TIAs in cases than controls. This would, however, not affect the main result in paper IV, which is the association between plaque echogenicity and clinical events, since the observer was blinded to the previous assessment of plaque morphology.

Confounding

When an association between an exposure and an outcome is distorted due to the effect of a covariate related to both the exposure and the outcome, this is called confounding.[90] An extraneous factor is mistaken for or mixed with the actual exposure effect on the outcome. Confounding may under- or overestimate the association under study, and may even change the direction of the effect.[90] If appropriate information about possible confounders is available, this can be accounted for in the analysis. Stratification by age and sex and multivariate-adjusted models with the inclusion of potential confounders are strategies that can be used to minimize bias due to confounding. Stratification by age and sex were used when studying prevalence of stenosis and stratification by sex was done in the analysis of risk factors associated with carotid stenosis (paper II), but the size of the study population was too small for further stratification in analyses of plaque morphology or categories based on stenosis severity. In these analyses, adjustments for age and sex and other possible confounders (e.g. the degree of stenosis when assessing the effect of plaque morphology on risk for cerebrovascular events in paper IV) were made by multiple linear, logistic or proportional hazards regression analysis.

5.1.2 External validity

The external validity of a study applies to whether the results are valid for people outside the population, other than the study population. The proportion of elderly people is relatively low in Tromsø due to high net immigration the last decades. Otherwise, the Tromsø population is similar to other inhabitants in Norway when it comes to incidence of cardiovascular disease, mortality, lifestyle, education and social factors,[107] and

probably not substantially different from other Western populations.

The population of Tromsø is of mixed Norse, Sami and Finnish origin. In the two first surveys of the Tromsø Study (1974 and 1979-80), participants were asked whether two or more of their grandparents were of Sami of Finnish origin. Information about ethnicity was thus available for 3754 of the 6727 subjects examined by ultrasound in the present survey. Seventy-eight % were of Norse decent, 4.5% of Finnish decent, 2.0% of Sami decent, and 0.7% were of both Sami and Finnish decent, while 15% did not know the ethnicity of their grandparents. There were no significant differences in prevalence patterns of carotid stenosis between persons of Sami, Finnish or Norse decent.

5.2. Discussion of main results

5.2.1. Definition and grading of stenosis

In a discussion on carotid stenosis, the definition of carotid stenosis is a crucial point. All previous studies on carotid stenosis prevalence have been ultrasound-based, but the methods used to assess stenosis vary, and different levels or cut-off points to define stenosis have been used (Table 2). Both the Framingham Study and the Bruneck Study used a combination of hemodynamic and B-mode criteria.[108-110] In the Kuopio Study[111] and the San Daniele Project[112] diameter reduction measured in the longitudinal plane was used, while the Rotterdam Elderly Study,[113] Jungquist et al.,[114] and Ricci et al.[115] used Doppler criteria. The Suita Study is the only one which has used B-mode area measurements in the cross-sectional plane.[116]

While a 5 % lumen reduction might be a meaningful definition of stenosis in an epidemiological setting (for instance when assessing the dose-response relationship between a risk factor and stenosis), this definition would hardly be meaningful in a clinical setting. In the Tromsø Study, we tried to define stenosis as the level of lumen reduction where hemodynamic changes could be detected. The peak systolic velocity begins to increase at approximately 30% – 35% lumen diameter reduction.[22; 117; 118] Thus, if the peak systolic velocity in the stenotic part (PSVs) was increased with respect to the peak systolic velocity at the point of reference (PSVr), we defined this as a stenosis.

However, when the stenosis is located to a part of the artery where the original lumen is wider than in the rest of the artery, hemodynamic changes can often not be detected. This was the reason why we used a cut-off point of 35% lumen diameter reduction in arteries where a lumen reduction of this size was seen in

Table 2. Prevalence of and risk factors for carotid stenosis in population-based studies

	Ultrasound method used for definition of stenosis	Age (years)	Number examined (attendance rate)	Cutoff	Prevalence (%) by age		Risk factors
					Men	Women	
The Kuopio Ischaemic Heart Study, Finland[111]	B-mode (diameter reduction)	42, 48, 54, 60	412 (84.1 %)	20%	42: 0 48: 0 54: 2.3 60: 4.8		LDL cholesterol, HDL
Umbria, Italy[115]	Doppler	≥50	320 (82.5 %)	16%	50-60: 8.4 61-70:21.5 >70:54.3	50-60:9.9 61-70: 25.1 >70:53.8	Age, hypertension
Malmö, Sweden[114]	Doppler (PSF, spectral broadening)	69	471 (77 %)	30% 60%	20 5		Smoking, triglycerides
The Rotterdam Elderly Study, Netherlands[113]	Doppler (PSF, spectral broadening)	≥55	954 (72 %)	≥50%	55-74: 2.4	55-74: 0.7	HDL, fibrinogen, smoking, hypertension
The San Daniele Project, Italy[112]	B-mode (diameter reduction)	18-99	1348 (74.9 %)	40%	<40: 0 40-49: 0.7 50-59: 0.9 60-69: 5.6 70-79: 18.8 80-99: 7.1	<40: 0 40-49: 0 50-59: 0 60-69: 2.9 70-79: 4.4 80-99: 12.1	Age, systolic BP, smoking, HDL cholesterol
The Cardiovascular Health Study, USA[119]	B-mode (diameter reduction) Doppler (PSVs)	≥65	5114 (57 %)	1-24% 25-49% 50-74% 75-99% occlusion	65-69: 4.4* 70-74: 7.2* 75-79: 9.4* 80-84: 11.8* ≥85: 14.3*	65-69: 4.3* 70-74: 4.1* 75-79: 6.6* 80-84: 7.7* ≥85: 11.5*	Age, sex, hypertension, smoking, diabetes, systolic BP, diastolic BP, cholesterol triglycerides, HDL, LDL, glucose, insulin
The Bruneck Ischemic Heart Study, Italy[110]	Doppler† B-mode (diameter reduction)	40-79	909 (93.6 %)	40%	40-49: 0 50-59: 4.3 60-69: 12.6 70-79: 14.6	40-49: 0 50-59: 0.9 60-69: 6.2 70-79: 9.7	Age, sex, systolic BP, smoking, fibrinogen
				80%	40-49: 0 50-59: 1.7 60-69: 4.2 70-79: 3.9	40-49: 0 50-59: 0 60-69: 1.8 70-79: 2.9	
The Framingham Study, USA[109]	B-mode Doppler†	66-93	1116 (not specified)	5-24% 25-49% ≥50	35 35 9	34 27 7	Age, smoking, cholesterol, systolic BP, alcohol‡
The Suita Study, Japan[116]	B-mode (area reduction)	50-79	1445 (not specified)	25-50%	50-59: 3.3 60-69: 7.9 70-79: 8.7	50-59: 0.3 60-69: 2.0 70-79: 11.8	Age, systolic blood pressure, smoking, cholesterol, HDL‡ glucose‡
				≥50%	50-59: 2.1 60-69: 7.6 70-79: 18.1	50-59: 0 60-69: 2.3 70-79: 1.6	
The Tromsø Study, Norway (paper II)	B-mode (diameter reduction) Doppler (PSVs/PSVr)	≥25	6727 (77 %)	35%	<50: 0 50-59: 1.7 60-69: 4.4 ≥70: 9.4	<50: 0 50-59: 1.1 60-69: 2.1 ≥70: 7.1	Age, sex, smoking, cholesterol, HDL cholesterol fibrinogen, systolic blood pressure

* for degree of stenosis ≥ 50 % (all age-groups)
† not specified
‡ men only

the bifurcation or the internal bulb, even if no increase in PSVs could be detected.

In a straight, continuous tube with constant volume flow, flow velocity is proportional to the cross-sectional area of the lumen. This is the theoretical basis for calculating the degree of stenosis from velocity measurements. Many laboratories use measurements of PSVs alone,[15; 120] others prefer velocity ratios.[12; 121] PSVs is easy to obtain and highly reproducible. The theoretical advantages of using a ratio, and not only the PSVs, is that this method can handle increased velocities due to stenosis or occlusion in the contralateral carotid artery and also individual day-to-day variations due to changes in cardiac output. The tradition in our laboratory and in many other cerebrovascular laboratories has been to use the distal internal carotid artery as the reference,[13; 35; 117] while others have used the common carotid artery.[12; 122] The major disadvantage of the common carotid artery is that it is does not meet the underlying assumption of a continuous tube as it also supplies the external carotid artery, which can show quite variable flow conditions. In this respect, the distal internal carotid artery is a better choice as it is continuos with the proximal part without any branching. The major disadvantage of the distal internal carotid artery is the narrower (and normal) lumen diameter with respect to the lumen in the internal bulb/the bifurcation-internal junction (Fig. 2, upper right panel). Thus, although a lumen diameter reduction of 30-40% is necessary to detect an increase in PSVs,[22; 117; 118] the calculated degree of stenosis can be considerably lower. This is why some of the estimated degrees of stenosis in Figures 2 and 3 in paper I are lower than the entry limit of 35%. In addition, the discrepancies between the different methods can result in the degree of stenosis being estimated above 35% by one method, but below by another.

The velocity method and the area method performed a little better than the diameter method as predictors of future cerebrovascular events, as the overall fit of the models with the velocity method or the area method was slightly improved compared to the model with the diameter method. As assessed by the log likelihood ratio method, the chi-squares were 11.06, 9.23 and 11.06, for the area, diameter and velocity methods, respectively. High quality area measurements were more difficult to obtain than velocity measurements, therefore, we chose the velocity method when the degree of stenosis was used as a covariate with plaque echogenicity in paper III and IV, and when assessing the dose-response relationship to risk factors in paper II.

Our ultrasound measurements have not been validated against cerebral

angiography, which makes it difficult to compare our results to studies based on angiographically defined stenosis. Even if the validity of both Doppler and B-mode assessments of carotid stenosis has been proved in numerous other studies, it is recommended that each laboratory does its own validation study.[123] However, to do a validation study where ultrasound is compared to angiography would mean subjecting participants to potential health risks, and we think this would have been unethical within the setting of a population-based study. The risks of angiography are not negligible,[124-126] and it is questionable how long cerebral angiography will hold its position of being the 'gold standard'.[21; 23] In many clinics, the combination of duplex scanning and MR or CT angiography have already replaced angiography.[16; 127]

The prevalence estimates in the oldest age-group (≥ 75 years), especially among men, are uncertain due to the low response rates, and also because the numbers are based upon 5 % samples of the population.

5.2.2 Reproducibility of plaque morphology

How reliable is assessment of plaque morphology? In the present study, the agreement above chance between two observers was assessed by the use of the kappa (κ) statistic. In all instances, the disagreements on plaque echogenicity were between "neighbour" categories (Table 3), thus, the weighted kappa (κ_w) value was 0.65 (95% CI 0.51-0.79), which can be characterized as substantial agreement. In a previous study based on the screening examination,[53] the agreement on off-line assessed plaque morphology was higher than in the present study where the scoring was done online (paper I). Since the majority of plaques in the first reproducibility study were non-stenotic, the difference could mean that the assessment of plaque morphology is less reliable in stenotic plaques. This has been suggested by Hartmann et al., who reported a kappa value of only 0.18 for plaque echogenicity assessments in 80-99% stenosis.[72] However, although keeping in mind the very low number of arteries in each category, the kappa-values in our study did not decrease by increasing degree of stenosis (for stenosis <50 % κ = 0.53, stenosis 50-69% κ = 0.58 and stenosis ≥70% κ = 0.76). We find it more likely that the lower reproducibility in paper II compared to our previous paper[53] can be explained by the higher chance of obtaining agreement when the same frozen images are assessed off-line by different readers, compared to on-line assessments, where variability both in obtaining and interpreting images influence the results.

Table 3. Classification of plaque echogenicity in 60 carotid arteries by two observers

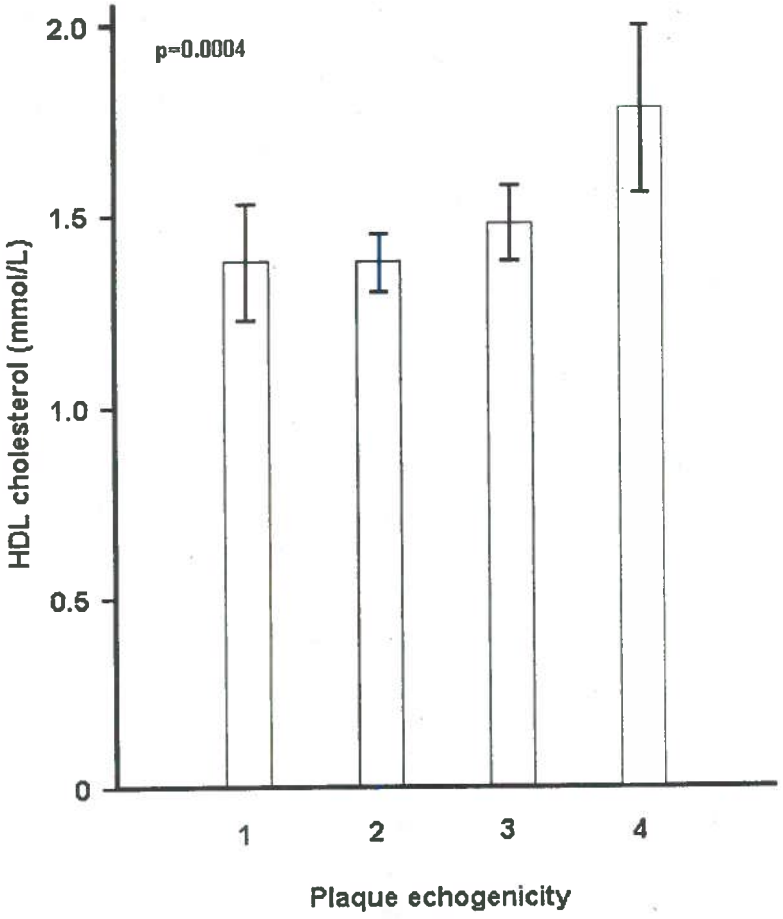
		Observer 1			
		Echolucent	Predominantly echolucent	Predominantly echogenic	Echogenic
Observer 2	Echolucent	4	1	0	0
	Predominantly echolucent	4	16	2	0
	Predominantly echogenic	0	7	21	2
	Echogenic	0	0	1	2

$\kappa_w = 0.65$ (95% CI 0.51-0.79)

5.2.3 Risk factors for plaque morphology

If some plaque types are at higher risk for rupture and thereby cause clinical events, it becomes important to find the risk factors associated with such plaques. In paper III, we found that HDL cholesterol was independently associated with plaque morphology (Figure 3). The results of multivariate statistical analyses including both triglycerides and HDL cholesterol may be difficult to interpret partly due to the metabolic inter-relationship between HDL and triglyceride-rich lipoproteins, and partly due to the mathematical problems of including two strongly correlated covariates in the same multivariate model.[128] In the present study, the coefficient of correlation between HDL and triglycerides was –0.41. An alternative approach would have been to exclude triglycerides from the multivariate analysis when HDL was the independent variable of interest, and vice versa. When this was done, both HDL (OR=0.64, 95% CI 0.49-0.84) and triglycerides (OR=1.37, 95% CI 1.05-1.78) were significantly related to plaque morphology (adjusted for age, sex, degree of stenosis and systolic blood pressure). We also tried a downward stepwise procedure with all 6 independent variables (age, sex, HDL cholesterol, triglycerides, degree of stenosis and systolic blood pressure) included at start, and the limits for removal from the model set at $p > 0.05$ and for re-entry into the model at $p < 0.05$. This procedure resulted in the removal of triglycerides and sex, while HDL cholesterol (OR=0.63, 95% CI 0.49-0.82, p=0.0005), systolic blood pressure (OR=1.36, 95% CI 1.04-1.77, p=0.02), degree of stenosis (OR=1.40, 95% CI 1.08-

Figure 4. Mean HDL cholesterol levels according to plaque morphology



Error bars represent 95% confidence intervals. *p*-value is for linear trend

1.82, p=0.02), and age (OR=0.73, 95% CI 0.56-0.96, p=0.03) were kept in the model.

While the effect of HDL on risk for cardiovascular disease is thought to be mediated through its role in reverse cholesterol transport,[129] many other effects of HDL on cellular processes have been shown,[130] and it is still not known whether HDL plays a causal role or not. The cross-sectional design in the present study does not allow inference about causality. However, animal studies have provided strong support for a causal relationship.[131]

Although triglycerides did not come out as an independent significant risk factor for plaque echogenicity when HDL was included in the multivariate model, this does not necessarily mean that triglycerides are unimportant. The combination of multicollinearity and the large intra- and inter-individual variability in triglyceride levels, can result in underestimating the risk associated with triglyceride level.[128; 132; 133] The large variability can partly be compensated for by repeated measurements, thus, we also tested whether the mean values of triglycerides and of HDL measured at the first and second visit performed differently than single measurements. In multivariate analysis with HDL, age, sex, degree of stenosis and systolic blood pressure as covariates, the OR for lower plaque echogenicity by one standard deviation (SD) increase in triglycerides was 1.18 (95% CI 0.88-1.59), and for one SD increase in HDL the OR was 0.72 (95% CI 0.53-0.97). Thus, the results were essentially the same as when single measurements were used. In studies on IMT from the Tromsø Study,[134] triglycerides were independently associated with IMT in women, but not in men. Lassila et al. reported that triglycerides were independently related to IMT in postmenopausal women.[135] Triglyceride level was an independent predictor for mortality from coronary heart disease, cardiovascular disease and any cause mortality among middle aged Norwegian women.[103] In our study, triglycerides were significantly associated with both the presence of and the degree of carotid stenosis in women and of borderline significance in men in univariate analysis, but not in multivariate analysis (paper II). In the Framingham Study, triglycerides were significantly related to the presence of carotid stenosis in univariate analysis, but not in a multivariate model which included HDL and total cholesterol.[109] Recently, a meta-analysis found a stronger association between triglycerides and cardiovascular risk in women than in men.[132] Unfortunately, the present study did not have power to address the relationship between triglycerides and plaque echogenicity in men and women separately.

High systolic blood pressure was associated with plaque echolucency. Hypertension is a well established risk factor for both atherosclerosis and stroke.[136; 137] Thus, it is not surprising that systolic blood pressure was related to the plaque type that was most likely to cause clinical events. However, our results are in conflict with those reported by Sillesen et al.,[45] who found that patients with arterial hypertension had less soft tissue in their plaques than normotensive patients. Duncan et al. found that hypertension was associated with acoustic shadowing of plaques.[74] As discussed in paper III, we were not able to reproduce the relationship between plaque echolucency and high systolic blood pressure when using morphology data from the screening. This issue needs further examination in future, preferably prospective studies.

5.2.4 Plaque morphology as a risk factor for cerebrovascular ischemic events

The limitations of the analytic possibilities of the present study lie mainly in the size of the study and the number of events that occurred in the follow-up period. This has made it necessary to make a pooled analysis of all cerebrovascular events and not only strokes or ipsilateral events/strokes. In an analysis of ipsilateral events, the control group can not be used as the reference since it is not possible to analyze ipsilateral events when no stenosis is present. In the Cox proportional hazards regression model with adjustments for age, sex, and degree of stenosis, the relative risk of ipsilateral events in the predominantly echolucent group was 3.52 (95% CI 1.0-12.42) and in the echolucent group 3.64 (95% CI 0.79-16.75, p for linear trend 0.097). In this model, the combined group of echogenic and predominantly echogenic plaques were treated as the reference, since there were no incidents in the echogenic group. If we follow the same procedure for all cerebrovascular events (that is, exclude the control group from the analysis and use the combined echogenic and predominantly echogenic group as the reference), we find that the adjusted relative risks for any cerebrovascular event are a little lower than for an ipsilateral event (in the predominantly echolucent group RR=1.82, 95% CI 0.82-4.01, in the echolucent group RR=2.60, 95% CI 0.98-6.93, p for linear trend 0.047). The data therefore clearly indicates that echolucent plaques are associated with risk of ipsilateral ischemic events.

It could be argued that although we found a clear trend towards higher risk for cerebrovascular events in echolucent plaques, what really matters is whether plaque echogenicity can predict stroke or not. The risk for stroke was significantly higher in the echolucent group in univariate

analysis, with a relative risk of 6.5 (95% CI 1.8-22.9). In multivariate analysis with plaque echogenicity, degree of stenosis, age and sex as independent variables, none of these variables were significant predictors of stroke. This is probably more a reflection of the low number of strokes (and subjects in each plaque category) in the study, rather than lack of real association. The relative risk of stroke for subjects with stenosis was significantly higher than in controls (RR=2.63, 95% CI 1.02-6.79), most of this effect was due to the higher proportion of stroke in the echolucent group.

In the present study, we categorized plaques both by their echogenicity and by hetero- or homogeneity. Homogeneity was closely correlated to plaque echolucency (r=0.88, p=0.0001), and categorizing plaques as either homogenous or heterogenous did not turn out to be helpful in predicting outcome.

Although the number of subjects in each category of plaque morphology was limited by the actual number of participants with stenosis in the Tromsø Study, the number of clinical events could have been increased by prolonging the follow-up period. This would increase the scientific value of the analyses, and should be performed in the future. However, subjects with stenosis in the present study have an increased mortality rate of causes other than ischemic stroke,[138] and this must be taken into consideration when determining the appropriate time for follow-up in order to avoid problems related to selective survival.

6. Conclusions and implications for further research

In the present study, we found that carotid artery stenosis is more common in men than in women, and increases with age. Variations in prevalence estimates between different centers are probably at least partly explained by variation in the definitions of the condition. The presence and degree of stenosis are associated with well established risk factors for cardiovascular disease. Variability in ultrasound-assessment of the degree of carotid stenosis can be considerable, especially in low-grade stenosis, and must be taken into consideration when this is of importance for clinical decisions. Although the assessment of plaque morphology by ultrasound is subject to variation, the reproducibility is acceptable. Plaque echogenicity can be used to predict outcome, and echolucent plaques are associated with a high risk for clinical ischemic events, independent of the degree of stenosis. The importance of determining risk factors for plaque echogenicity lies in the potential for finding preventive measures that can influence plaque echogenicity and thereby reduce the

risk of clinical events. High HDL cholesterol levels are associated with a plaque type that seems to be stable and at lower risk of stroke, indicating that prophylaxis aimed at modulations of HDL levels might be an important target for antiatherosclerotic drug therapy.[129; 139]

Computer-quantification based on integrated backscatter digital densiometric analysis[73;140;141] is a more objective method of ultrasonic plaque characterization, which probably will improve the ultrasound assessment of carotid plaques morphology. Further improvements have been reported with use of three-dimentional ultrasound.[142] Other promising imaging techniques are magnetic resonance imaging[143; 144] and optical coherence tomography.[145] These techniques might be superior to present ultrasound techniques. The feasibility of the present subjective ultrasound-assessment of carotid plaques lies in its already wide-spread use, the equipment is relatively cheap, it can easily be transported, which makes it suitable for the whole scale of indications for carotid imaging; from bed-side clinical examinations of patients to larger studies of patient cohorts and populations.

The fact that plaque echogenicity can be used to predict outcome indicate that subjective assessment of plaque morphology by ultrasound has the potential of being a clinically relevant and useful procedure. Although careful training and practice are required, it should be possible to assess plaque morphology in every-day clinical practice. What then should the implications of finding an echolucent plaque be? We think that the presence of an echolucent plaque, especially if combined with a high degree of stenosis, makes a careful follow-up and treatment warranted, with, if possible, eradication of other risk factors, regardless of whether the patient has symptoms or not. Whether medical or surgical treatment will be of highest benefit, remains to be seen, although prophylactic surgery on those that have the combination of an advanced stenosis and an echolucent plaque feels like an attractive choice. In a recent publication from the European Carotid Surgery Trial, an increased relative risk of stroke was found in baseline symptomatic patients with plaque surface irregularity on carotid angiograms, as compared to symptomatic patients with a smooth plaque surface.[146] The risk of stroke was higher for those who had plaque surface irregularity at baseline and were treated medically than for those in the endarterectomy group. Although surface irregularity describes another quality of plaque morphology than echogenicity, it is possible that echolucent plaques are likely to appear as irregular on angiograms, since these plaque characteristics both are associated with plaque rupture and clinical

events. If echolucent plaques are over-represented among those plaques which appear as irregular on angiograms, this implies that endarterectomy will be beneficial in symptomatic echolucent plaques, independent of degree of stenosis. Lipid-lowering therapy is another approach. Treatment with pravastatin for 3 months prior to endarterectomy in patients with symptomatic carotid stenosis was found to decrease lipid content, lipid oxidation, inflammation, metalloproteinase 2 and cell death and increased collagen content and tissue inhibitor of metallo-proteinase 1 in the carotid plaque.[147]

A recent prospective study on patients with acute myocardial infarction, showed that the presence on angiography of multiple complex plaques in the coronary vasculature was associated with increased incidence of acute coronary syndromes, repeated angioplasty, and coronary by-pass surgery, as compared to single complex plaques.[148] Rothwell et al. showed that carotid artery plaque surface irregularity, as measured on carotid angiography, was associated with increased risk of coronary heart disease.[149] These findings suggest that carotid and coronary artery plaques may share morphologic characteristics within individuals, and that in some individuals, plaque instability may be a widespread, systemic process. If this hypothesis is correct, assessment of plaque morphology in carotid arteries may be of potential value not only for predicting risk of future ischemic stroke, but also acute coronary events.

The present study addressed the importance of plaque morphology in subjects with advanced atherosclerotic lesions. It remains to be seen whether plaque morphology is a predictor of cerebrovascular events also in subjects with non-stenotic plaques. The fifth survey of the Tromsø Study is scheduled to start in March 2001. All those who were examined with ultrasound of the carotid arteries in 1994-95, will be invited to a new ultrasound examination of the carotid arteries. The design of the study will be similar to the last survey, with the addition of several genetic tests which will be performed on samples of the study population. The latter is the result of our participation in a European multicenter study on genetic and lifestyle factors and the risk for myocardial infarction and stroke (the GENERALE Study). This will enable us to study the genetic and environmental risk factors associated with the development and morphology of new plaques, changes in plaque morphology, the progression or regression of carotid plaques and stenosis, and whether such changes are associated with clinical outcome.

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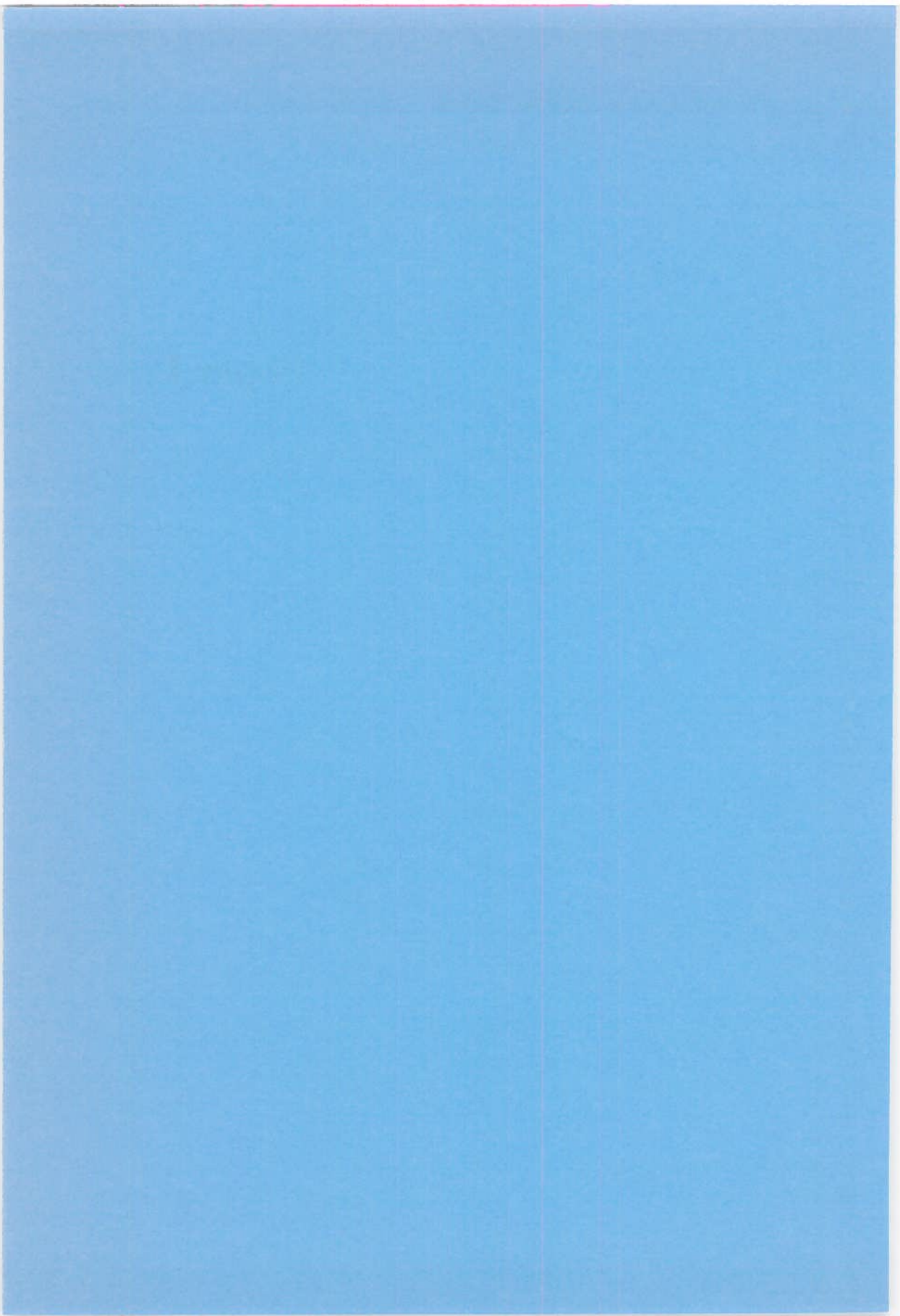
Paper I



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Intersonographer Reproducibility and Intermethod Variability of Ultrasound Measurements of Carotid Artery Stenosis: The Tromsø Study

Ellisiv B. Mathiesen Oddmund Joakimsen Kaare H. Bønaa

Institute of Community Medicine and Institute of Clinical Medicine, University of Tromsø, Norway

Key Words

Reproducibility · Ultrasonography · Carotid stenosis · Atherosclerosis

Abstract

Background and Purpose: Knowledge of the reproducibility of a diagnostic method is important in order to evaluate its usefulness. Few studies have examined interobserver and intermethod agreement on ultrasound measurements of carotid stenosis. ***Methods:*** Intersonographer agreement on ultrasound measurements of carotid plaque morphology and the estimated degree of stenosis by three ultrasound methods were assessed in a random sample of 51 participants with stenotic carotid arteries selected from a population health survey. The degree of stenosis was assessed by measurements of velocity, lumen diameter reduction and cross-sectional lumen area. Intermethod agreement on the degree of carotid stenosis was also assessed. ***Results:*** Agreement on plaque echogenicity and heterogeneity was moderate ($\kappa = 0.56$ and $\kappa = 0.60$, respectively). The mean degree of stenosis and median absolute difference between observers of the estimated degree of stenosis by the velocity method were 46.3 and 10.8%, respectively. The corresponding values were 51.0 and 5.8% for the diameter method, and 57.1 and 7.2%, for the cross-sectional lumen method. The limits of agreement for intersonographer reproducibility varied between ± 19.7 and 26.5%. For all methods, reproducibility increased with increasing degree of stenosis. Differences between the methods were large in low-grade stenosis but were acceptable in high-grade stenosis. ***Conclusions:*** Considerable differences in ultrasound measurement of stenosis, which could lead to different clinical conclusions, were regularly encountered no matter what ultrasound method was used.

Ultrasonography of the carotid arteries has over the last decades become the most frequently used method for the diagnosis of extracranial carotid artery disease. Although angiography is still in most centers considered mandatory before carotid endarterectomy, ultrasonography forms the base upon which the decision to perform angiography or not is made. Routine ultrasonography of the carotid arteries is not, however, a well-defined procedure. Both B mode and Doppler velocity measurement techniques are subject to considerable methodological variation.

Two aspects are of interest when examining the usefulness of a diagnostic test, essentially the *validity* of the test, i.e. whether the test results correspond to the biological

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Ellisiv B. Mathiesen
Institute of Community Medicine, University of Tromsø
N–9037 Tromsø (Norway)
Tel. +47 77 64 64 18, Fax +47 77 64 48 31
E-Mail Ellisiv.Mathiesen@ism.unit.no

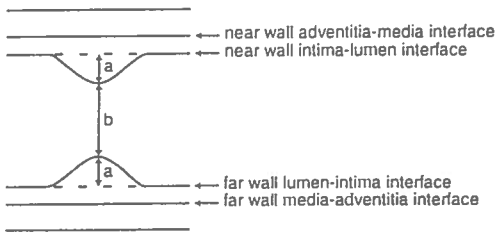

Fig. 1. Schematic drawing of carotid artery stenosis: a denotes plaque thickness, b denotes residual lumen diameter, a + b = total lumen diameter.

truth or, more often, a gold standard, and the *reproducibility* of the test, i.e. the probability of obtaining the same reuslts in the same subject when the test is repeated. The validity of ultrasonography has been examined against angiography and, less often, against pathology specimens in numerous studies. Surprisingly, the reproducibility of ultrasonography in measuring the degree of stenosis has not been investigated thoroughly, and the results are difficult to interpret and partly contradictory [1–8]. The purpose of this study was to evaluate interobserver agreement with three different ultrasound methods for the calculation of the degree of stenosis, to assess the agreement between the methods and to assess the reproducibility of measurements of plaque morphology of stenotic plaques.

Material and Methods

Material

In 1994/1995, all inhabitants older than 24 years living in the municipality of Tromsø, Norway, were invited to participate in a health survey. Details of the study design have been presented previously [9, 10]. All participants aged 55–74 years and random 5 to 10% samples in the other 5-year age groups were offered an ultrasonographic examination of the right carotid artery, and 6,727 subjects, 88% of those who were eligible, attended. Of these, 784 persons also had their left carotid artery examined.

Stenosis of the carotid artery was considered to be present if one or both of the two following criteria were met: (1) peak systolic velocity in the tightest stenotic part (PSV_s) ≥ 0.2 m/s higher than peak systolic velocity at the point of reference (PSV_r), or ≥ 0.1 m/s if the stenosis was located to the bifurcation or the bulb of the internal carotid artery; the distal part of the internal carotid artery (with parallel walls) was used as the point of reference; (2) 35% or more reduction in lumen diameter on a longitudinal B mode scan. Two hundred and thirty-one persons were diagnosed as having stenosis of the carotid bifurcation and/or internal carotid artery, and participated in a prospective follow-up study with annually repeated ultrasound examinations. A random sample of 51 persons with stenosis of the carotid artery was selected for the present study. The main objective of the reproducibility study was to assess between-observer and between-method variability of three different ultrasonographic methods for measuring the degree of stenosis. The study was also designed to assess the variability of measurements of plaque echogenicity and heterogeneity of stenotic plaques.

Each participant was examined consecutively by two observers who used the same ultrasound scanner, with just a few minutes between each session. The sonographers were blinded to each other's results. Both observers were neurologists who had more than 10 years' experience with ultrasound examinations of carotid arteries.

Methods

High-resolution B mode and color Doppler/pulsed-wave Doppler ultrasonography of both carotid and vertebral arteries was performed with an ultrasound scanner (Acuson Xp10 128 ART) equipped with a linear-array 5- to 7-MHz transducer. Instrument imaging adjustments (preprocession and postprocession, persistence, log compression, image depth) were set at fixed values. The gain setting (including the depth gain compensation curve) and transmit zones were adjusted in each individual to obtain optimal visualization of arterial wall morphology. The gain setting was also continuously changed during the scanning procedure on the same individual to enhance plaque detection and characterization. Calculation of velocity is highly dependent on the cosine of the angle of the Doppler beam on the axis of the vessel. This angle was not fixed, but was not allowed to exceed 60°. The angle correction function of the Acuson instrument allows correction of the angle between the incident Doppler beam and the axis of the blood vessel by compression of the velocity scale. No fixed angle of interrogation was used, the investigators tried to view the arteries from all possible angles and determined the angle that best demonstrated the stenosis in each subject. The subjects were examined in the supine position with the head slightly tilted to the opposite side. The common, internal and external carotid arteries and vertebral arteries were identified by combining B mode and color Doppler/pulsed-wave Doppler ultrasound. The common carotid artery (CCA) was defined distally by the point where the parallel lines of the walls started to diverge, the bifurcation was defined from the point where the parallel lines of the CCA start to diverge and to the tip of the flow divider, and the internal carotid artery was defined from the tip of the flow divider and distally.

All measurements were made on-line by the sonographers (i.e. no extra reader step was involved). Printed images of all measurements were made for later documentation.

Plaque thickness and lumen diameter (i.e. the original lumen diameter) at the point of maximum stenosis were measured on-line on frozen B mode images marked with electronic calipers with measurement readouts in tenths of a millimeter. We tried to achieve the chord of greatest length, which means the true full diameter of the vessel, i.e. both near and far wall intima-media complexes should be visible and the plaque should be continuous with the intima-media structure on both sides of the plaque. Plaque thickness in the far wall was defined as the distance between the leading edge of the lumen-plaque interface and the leading edge of the media-adventitia interface – the intima-media thickness, i.e. the protruding part of the plaque into the vessel lumen (fig. 1). In the near wall, plaque thickness was defined as the distance between the leading edge of the intima-lumen interface and the far edge of the lumen-plaque interface.

Table 1. Between-observer variability of ultrasonographic measurements in stenotic internal carotid arteries

	Arteries	Mean	Arithmetic difference		Absolute difference		Limits of agreement
			mean	95% CI	mean	median	
Plaque thickness, mm	60	3.52	−0.22	−0.48, 0.05	0.77	0.50	± 1.96
Lumen diameter, mm	60	6.95	−0.32	−0.61, −0.04*	0.91	0.80	± 2.19
PSV_s, m/s	60	1.39	0.05	−0.04, 0.15	0.22	0.15	± 0.71
PSV_r, m/s	60	0.60	0.07	0.03, 0.11*	0.13	0.12	± 0.30
Measures of stenosis, %							
Diameter method	60	51.0	−0.4	−3.0, 2.2	7.6	5.8	± 19.7
Area method	52	57.1	−1.8	−5.2, 1.7	9.5	7.2	± 24.3
Velocity method	60	46.3	−3.8	−7.3, −0.3*	11.4	10.8	± 26.5

* $p < 0.05$.

The original longitudinal lumen diameter was measured according to the same principles, and this diameter is used as the denominator in the calculation of the degree of lumen diameter reduction.

Cross-sectional lumen area and plaque area were measured on frozen B mode images of the vessel visualized in the axial plane. B mode was combined with color Doppler ultrasound in order to enhance visualization of the plaque area. Lumen and plaque areas were computed after the outlines of the lumen and the plaque (alternatively the residual lumen) had been marked on-line by using an electronic drawing program.

The degree of stenosis was calculated by the following equations: (1) lumen diameter reduction = (plaque thickness/lumen diameter) × 100%; (2) cross-sectional lumen area reduction = (plaque area/lumen area) × 100%; (3) peak systolic velocity ratio method: $(1 - PSV_r/PSV_s) \times 100\%$.

In the following, the three methods will be referred to as the diameter method, the area method and the velocity method.

Plaque morphology in terms of ultrasound echogenicity was graded from 1 to 4, where grade 1 denotes echolucency and grade 4 denotes strong echogenicity, and was also classified according to structural appearance criteria as either heterogenous or homogenous, as described previously [10]. The study was approved by the regional ethical committee.

Statistical Analysis

Between-sonographer variability of measurements of plaque thickness, lumen diameter, V_s, V_r and the three different methods for calculating the degree of stenosis was estimated by calculating the mean arithmetic and mean and median absolute differences between repeated measurements on the same subject. Agreement plots according to Bland and Altman [11] were constructed. Any systematic differences between observers would result in the mean of the differences being significantly different from zero. The wider the scatter between the points in the direction of the y-axis, the worse will be the agreement. If the differences are normally distributed, 95% of the differences will lie within a range of ± 1.96 SDs of the mean arithmetic difference. This range will be referred to as the limits of agreement. The mean or median absolute difference represents the typical magnitude, although not the 'direction' of the differences. Variability of categorical data was analyzed with the use of the κ statistic [12]. κ measures the agreement that occurs above change and may have values between −1 (complete disagreement) and +1 (perfect agreement). κ values from 0 to 0.20 are categorized as slight agreement, values from 0.21 to 0.40 as fair, those from 0.41 to 0.60 as moderate, from 0.61 to 0.80 as substantial, and values of 0.81 and above indicate almost perfect agreement. The 95% confidence intervals (CIs) were estimated as κ estimates ± 2 SE. Means were compared with the use of Student's t test. Differences between proportions were analyzed by the χ^2 test. Two-sided values of $p < 0.05$ were considered statistically significant. The SAS software package was used [13].

Results

The sex distribution (60.9% men), mean age (65.1 years) and mean body mass index (26.8, i.e. weight/height^2) of the 51 participants in the reproducibility study were similar to those of the total population with stenosis (n = 232). Eleven participants had bilateral stenosis. In these subjects agreement on the various ultrasound assessments in the two arteries may be interdependent. We therefore first analyzed the data separately for only one stenotic artery per person. The results were essentially the same when bilateral stenoses were included in the analysis; thus, in the following, results are presented for all stenotic arteries (n = 60).

Agreement on plaque thickness and lumen diameter is shown in table 1. The mean arithmetic difference of plaque thickness was small, 6.5% of mean plaque thickness. Observer 1 generally measured both greater plaque thickness and lumen diameter than observer 2: 3.63 and 7.11 mm, respectively, and 3.41 and 6.79 mm, respectively. For lumen diameter, the between-observer difference was significantly different from zero. There was no significant difference between the two observers for the mea-

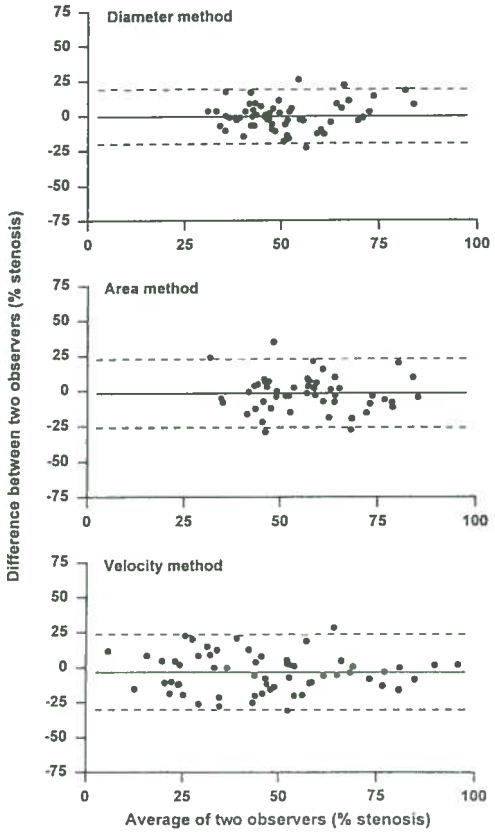

Fig. 2. Plots of intersonographer reproducibility of ultrasound-assessed stenosis. All panels show the difference against the average of two sonographers by the use of the three methods for assessing the degree of carotid artery stenosis. Solid lines denote the average difference and dotted lines denote the limits of agreement.

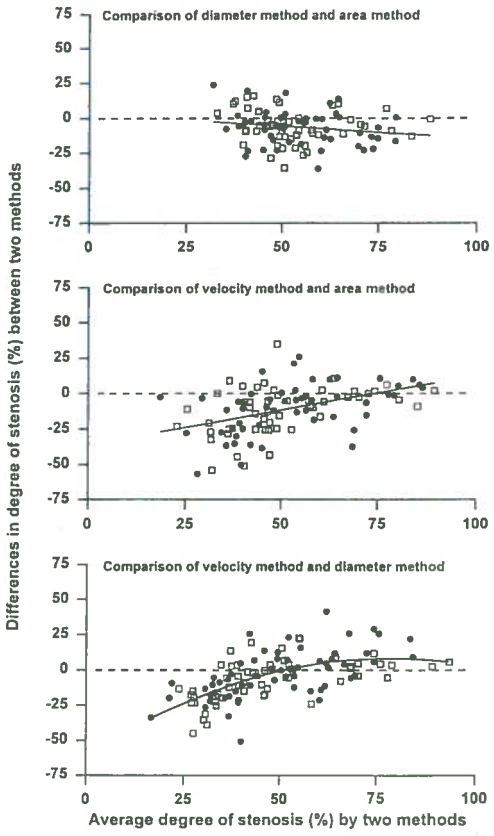

Fig. 3. Plots of intermethod reproducibility of ultrasound-assessed stenosis. Differences between two methods (y-axis) are plotted against the average of the two methods (x-axis). In the top panel, the y-axis shows diameter method minus area method, in the middle panel the y-axis shows velocity method minus area method, and in the bottom panel velocity method minus diameter method. The solid lines denote the regression lines for each plot. Filled circles represent one sonographer, open squares the other.

surement of stenosis by the diameter method. We were not able to obtain high-quality cross-sectional measurements in 8 (13.3%) of the stenotic arteries. In the remaining 52 arteries, the area method gave similar between-observer absolute differences in the estimated degree of stenosis as the other two methods. Mean arithmetic differences for PSV_s were small and not significant, whereas variability was significant for PSV_r. When calculating stenosis by the velocity ratio method, V_r is the numerator and V_s the denominator. Mean degree of stenosis according to this method was 44.4%, with a mean arithmetic difference of −3.8% (not significant) and a mean absolute difference of 11.4%.

Figure 2 shows the agreement between observers for the three different methods for measuring degree of stenosis. For the area method, variability was relatively constant throughout the range of stenosis levels. For the two other methods, reproducibility tended to be better at higher levels of stenosis.

Agreement on the presence of occlusion of the internal carotid artery was almost perfect, as both observers agreed that 5 (of 102 possible) internal carotid arteries were occluded but disagreed in one instance ($\kappa = 0.88$, 95% CI 0.69–1).

The relationship between the different methods for calcualtion of stenosis is shown in figure 3. For the velocity method, the relationship to the area method was linear, whereas that to the diameter method was parabolic. The differences between the velocity method and the diameter method, and between the velocity method and the area method tended to be greater in low-grade stenoses ($p = 0.0005$ and $p = 0.0001$, respectively). That is, in stenosis <50%, the velocity method generally estimated lower degrees of stenosis than the diameter method and the area method. No such correlation was observed for the differences between the diameter method and the area method.

Table 2 shows the κ values for interobserver agreement for the three different methods at various cutoff points of stenosis. For all methods, reproducibility increased with increasing degree of stenosis, most markedly for the velocity method. With the use of a 70% cutoff, the number of disagreements was 3 with the velocity method, 4 with the diameter method and 7 with the area method.

Agreement on plaque morphology is shown in table 3. Agreement on 4 categories of echogenicity was moderate ($\kappa = 0.56$). Merging echogenicity grades 1 and 2 into one category (low echogenicity) and grades 3 and 4 into another (high echogenicity) resulted in substantial agreement ($\kappa = 0.70$). The κ value for plaque heterogeneity was 0.60.

Table 2. Between-observer agreement of categories of stenosis dichotomized at various cutoff points for three different methods for assessment of stenosis

Stenosis	κ	95% CI	Disagreements
Diameter method[1]			
50%	0.53	0.28–0.78	14
60%	0.61	0.36–0.86	9
70%	0.68	0.43–0.93	4
Area method[2]			
50%	0.43	0.18–0.68	16
60%	0.38	0.13–0.63	17
70%	0.60	0.36–0.84	7
Velocity method[1]			
50%	0.57	0.33–0.81	13
60%	0.66	0.41–0.91	8
70%	0.79	0.54–1.0	3

[1] n = 60 arteries.
[2] n = 52 arteries.

Table 3. Between-observer agreement on plaque echogenicity and heterogeneity

	Arteries	κ	95% CI
Echogenicity – 4 categories	60	0.56	0.38–0.74
Echogenicity – 2 categories	60	0.70	0.45–0.95
Heterogeneity	60	0.60	0.36–0.84

Discussion

For all three methods used to estimate the degree of stenosis and at all levels of stenosis, sizeable differences did occur between observers. Our findings may have implications for both research and routine clinical practice by illustrating the uncertainty of current ultrasound techniques. The limits of agreement indicate that an increase in stenosis of as much as 20–27% can be attributed to measurement error, even if the measurements are made by experienced sonographers. However, as the κ analysis in table 2 shows, disagreements were most pronounced for the lower degrees of stenosis. This analysis was made in an attempt to measure the clinical consequences of the variability. The κ results are, however, dependent on the prevalence. With more stenoses at or around the cutoff, it is likely that these numbers would have been higher.

The magnitude of interobserver variability seen in our study is not unique for ultrasound estimates of carotid stenosis. In a study of four different methods for grading of stenosis by digital subtraction angiography, Young et al. [14] found median absolute differences between observers ranging from 5 to 8%, and 95% limits of agreement ranging from between –12 and 25 to –13 and 28.

In our study, reproducibility was lowest for the velocity method. Previous studies have found interobserver variability of various Doppler velocity or frequency measurements in the carotid artery to be good [1, 4, 6, 7]; however,

in these studies the coefficient of correlation was used as an indicator of agreement. The coefficient of correlation is not the appropriate statistical parameter for assessment of agreement, since even a high coefficient of correlation can conceal a considerable lack of agreement [11]. Kohler et al. [3] found κ values for intersonographer and interreader variability in 5 disease groups of stenosis of 0.54 and 0.61, respectively. Mikkonen et al. [5] found significant differences between 9 and 12 observers, who repeatedly measured PSV in the CCA in one healthy subject, and concluded that Doppler ultrasound measurement 'is not reliable and that its use should perhaps be avoided'. PSV was not measured at a fixed distance from the bifurcation, however, and this could have contributed to the poor results since it has been shown that velocities in the CCA vary depending on the distance from the bifurcation [15].

PSV_r measurements varied considerably and this was the most important contributor to the variability of the velocity method. Measuring PSV_r at a fixed distance from the stenosis may have led to less variability [16]. However, if the distance is set too short, one risks measuring PSV_r in the stenotic area in the case of elongated stenosis, or, if the distance is set too long, it may be impossible to measure PSV_r since the distal part of the artery is usually located deeper in the neck.

Several laboratories use PSV_s alone as predictor of the degree of stenosis, and, based on reproducibility, PSV_s was superior to the velocity ratio method in our study. It has been shown, however, that PSV_s varies considerably depending on the ultrasound equipment and is also subject to variability on repeated measurements in the same individual. This problem can be avoided by the use of velocity ratios. The free choice of angle of the Doppler beam to the axis of the vessel, although not allowed to exceed 60°, might obviously be another source of variability in the estimation of velocity. The use of a fixed angle could, however, lead to uncertainty about whether the measured velocities were a reflection of the true velocities or not.

Several factors may affect agreement on B-mode-assessed stenosis in a longitudinal cut. Differences in measurements of plaque size have been shown to increase with increasing plaque thickness [10]. Another source of variability is the angulation of the probe. Stenotic plaques are usually axiasymmetrical, which means that different views of the artery might show different degrees of stenosis [17]. In most studies, the intima-media thickness has been included in measurements of lumen diameter and plaque thickness. We chose not to include the intima-media thickness in the lumen measurements, partly because it is not part of the true lumen and partly to avoid bias when a lesion was present in only one of the walls, since intima-media thickness would then be counted once in the plaque thickness estimate but twice in the estimation of total lumen. However, excluding the intima-media complex from the measurement might lead to a more random positioning of calipers and thus to greater variability.

Reproducibility of plaque morphology has been found to vary, ranging from fair to substantial [10, 18–21]. Reproducibility of plaque morphology in the present study is lower than in our previous study [10]. One reason may be that the previous study was based on off-line reader assessment, while the present one was made on-line.

Fabris et al. [22] reported interobserver reproducibility of the degree of stenosis based on cross-sectional measurements, as measured by a mean coefficient of variation of 7.4% for the difference between repated measurements. In our study, the area method was similar to the two other methods in terms of reproducibility. An advantage of the area method is that it is less dependent on the angle of interrogation. However, although the addition of color Doppler ultrasound is helpful, the outlines of the original and residual lumens are often not easily defined. As with longitudinal images, results are dependent on when in the cardiac cycle measurements are made. This is not only due to variation in lumen size, but also due to variations of color overlap throughout the cardiac cycle. In our experience, high-quality cross-sectional images are harder to achieve than longitudinal ones.

Since blood velocity is inversely proportional to lumen area, a better agreement between the velocity method and the area method than between the velocity and diameter methods was to be expected. When atheroma produces approximately 30–40% bulb diameter reduction, it corresponds to more than 50% area stenosis, and PSV increases abruptly [23]. The velocity method applies to a situation where the stenosis is situated in between two straight tube segments, with the underlying assumption that the original lumen in the stenotic part is the same as in the distal part. As known, this is usually not the situation in proximal internal carotid stenosis since the lumen in the internal bulb and in the bifurcation-internal junction is wider than in the distal part of the internal carotid artery. This may lead to systematic error where PSV_s might be the same or even lower than PSV_r in cases of low-grade diameter stenosis. The diameter method is comparable to angiography, which also bases estimation of level of stenosis on diameter reduction.

We conclude that considerable differences in the reproducibility of ultrasound measurement of stenosis, which could lead to quite different clinical conclusions, are regularly encountered no matter what ultrasound method is used. We do not believe that the differences are sufficient to say that one technique is better than the other. When degrees of stenosis are found at or around the cutoff points for important clinical decisions, efforts should be made to ensure that the measurements are as accurate as possible. This could be obtained by making repeated measurements by one or more sonographers. We believe that it is important to use all available information from the ultrasound examination; combining velocity criteria with a high-quality visualization of the stenotic channel in B mode and color Doppler ultrasound offers the best method to ensure reliability. However, it remains to be determined which combinations of methods would be the best for identifying the defined degrees of stenosis upon which therapeutic decisions can be based.

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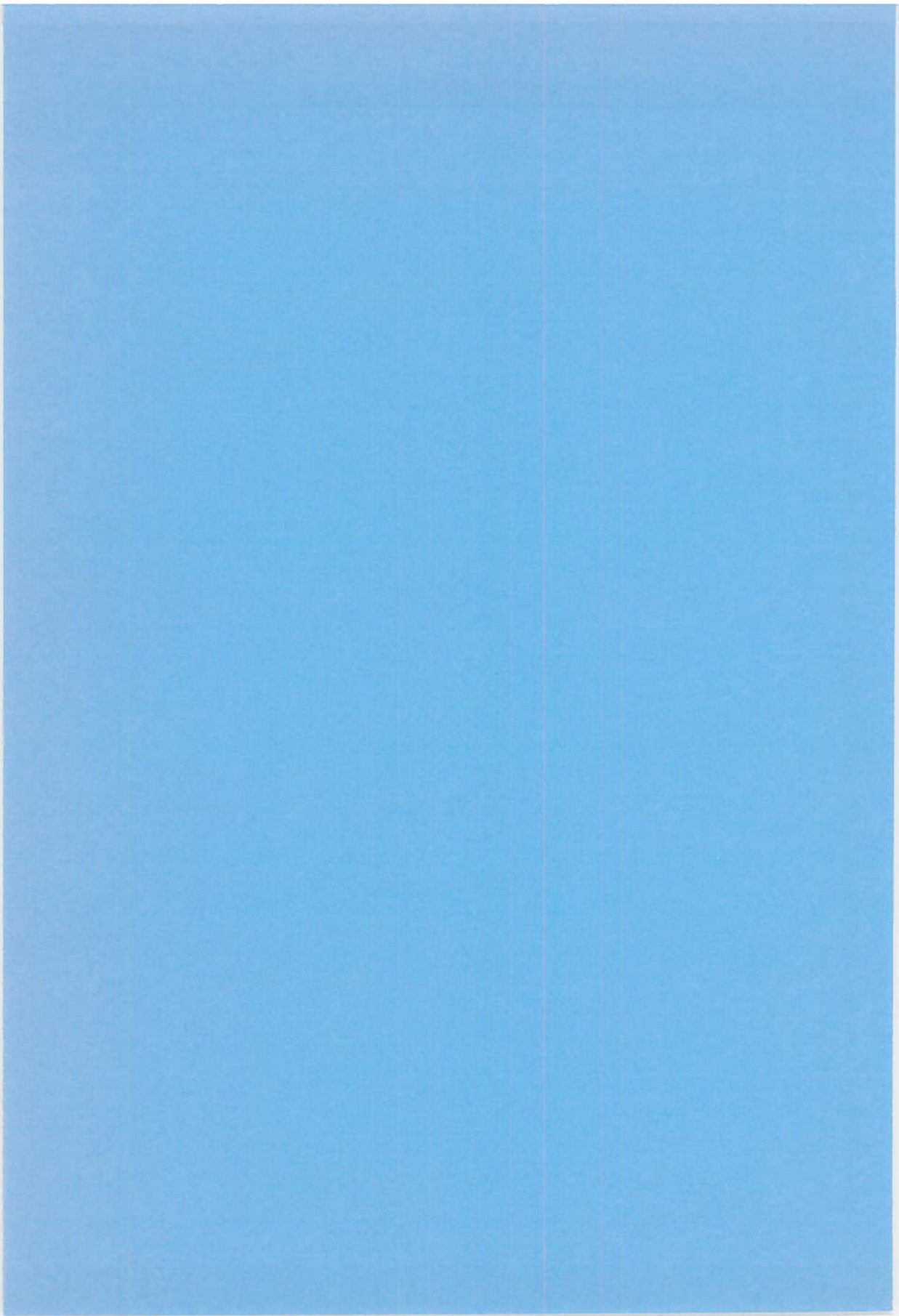
Paper II



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Prevalence of and Risk Factors Associated with Carotid Artery Stenosis: The Tromsø Study

Ellisiv B. Mathiesen Oddmund Joakimsen Kaare H. Bønaa

Institute of Community Medicine and Institute of Clinical Medicine, University of Tromsø, Norway

Key Words
Carotid stenosis · Risk factor · Prevalence

Abstract
Background and Purpose: To assess prevalence, distribution, ultrasound characteristics and determinants of carotid artery stenosis in a large, population-based study of both women and men. ***Methods:*** A total of 6,727 persons aged 25–84 years were screened for extracranial stenosis with Duplex ultrasound of the right carotid artery. Risk factors were compared in 225 persons with stenosis and 5,514 persons without. ***Results:*** The prevalence of carotid stenosis was higher in men than in women, where 3.8% (95% CI, 3.2–4.6%) had carotid stenosis, compared to 2.7% (95% CI, 2.2–3.3%) in women ($p = 0.001$). The prevalence gradually increased by age in both genders. Cholesterol, HDL cholesterol, fibrinogen, systolic blood pressure levels and current smoking were independently associated with carotid artery stenosis in both women and men. The presence of carotid stenosis was significantly associated with a history of cerebrovascular disease, coronary heart disease and peripheral artery disease. For each 10% increase in the degree of carotid stenosis, the risk of having had a cerebrovascular event increased by 26%. ***Conclusions:*** The prevalence of carotid stenosis in the general population, as measured by ultrasound, is low. Age, male gender, smoking, total cholesterol, HDL cholesterol (inverse), fibrinogen and systolic blood pressure are all independent predictors of carotid artery stenosis.

Noninvasive ultrasound examination of carotid arteries has made screening for carotid artery disease possible. The prevalence of carotid artery stenosis in the general population has been examined in previous studies [1–10]; however, some of these are small [1, 3, 4], some are limited to selected age groups [3, 10], and some have only included men [1, 3]. The purpose of this study was to assess prevalence of ultrasound-detected extracranial carotid stenosis in an adult population of both women and men in a broad age span, and to investigate risk factors associated with carotid stenosis.

Subjects and Methods

Subjects

The Tromsø Study was started in 1974 and is a single-center study of inhabitants in the municipality of Tromsø, Norway. The study design includes repeated population health surveys to which total birth cohorts and random samples of other age groups are invited [11]. The main focus is on cardiovascular diseases.

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Ellisiv B. Mathiesen
Institute of Community Medicine, University of Tromsø
N–9037 Tromsø (Norway)
Tel. +47 77 64 64 18, Fax +47 77 64 48 31
E-Mail ellisiv.mathiesen@ism.uit.no

The fourth survey of the Tromsø Study started in September 1994 and was completed in October 1995. The survey was conducted by the University of Tromsø in cooperation with the National Health Screening Service, and comprised two screening visits 4–12 weeks apart. All inhabitants older than 24 years living in the municipality of Tromsø were invited to the first visit, and a total of 27,159 subjects, 77% of the eligible population, attended. The protocol for the first visit was similar to the previous surveys in this population [12], and included standardized measurements of height, weight, blood pressure, and nonfasting serum lipids. Two self-administered questionnaires, checked by trained nurses, comprised information about smoking habits, use of drugs, previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (all yes/no) and treated hypertension (never/previous/current). Height and weight were measured in light clothing without shoes; body mass index was calculated as weight per squared height (kg/m^2). Blood pressure was recorded by the use of an automatic device (Dinamap Vital Signs Monitor) in a separate, quiet room by a specially trained nurse. After the participants had been seated for 2 min, three recordings were made at 2-min intervals. The mean of the two last values is used in this report. Nonfasting serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer-Mannheim). Serum high-density lipoprotein (HDL) cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. Fibrinogen was measured using the PT-fibrinogen reagent (Instrumentation Laboratory, Italy). Glycosylated hemoglobin levels were measured by a liquid chromatographic procedure (Diamet™ system; Bio-Rad Laboratories GmbH, Munich, Germany). White blood cell count was measured by the Coulter method on a Coulter Counter S-Plus STKR analyzer (Coulter Electronics Ltd., Luton, UK). All analyses were performed at the Department of Clinical Chemistry, University Hospital of Tromsø.

All subjects between 55 and 74 years and random 5–10% samples of subjects in the other age groups were invited to the second visit. A total of 6,889 subjects attended, 79% of the eligible population. The second visit comprised ultrasonographic examination of the right carotid artery, measurements of waist and hip circumference, sitting and standing blood pressures, and repeated measurement of nonfasting serum lipids. Ultrasonography of the right carotid artery in the neck was performed on 6,727 persons; among these, both the right and left carotid artery were examined in 784 persons. The examination of only one carotid artery was done for logistical and economical reasons. The second visit also included a selected group of 308 high-risk men aged 40–54 years, 6 of them with stenosis of the right carotid artery, who had previously taken part in a dietary intervention trial [13]. Since we wanted the results to be representative for the general population, this selected group was excluded for the purpose of this paper.

All persons with suspected stenosis or occlusion of one or both internal carotid arteries were offered referral to the Department of Neurology, The University Hospital of Tromsø, for participation in a follow-up study. The sonographers tried to achieve a high sensitivity, and accordingly referred cases where scanning was difficult or when they were in doubt about whether the criteria for stenosis were fulfilled or not, e.g. when calcified near wall plaques caused acoustic shadowing of the vessel lumen. A total of 242 persons with suspected stenosis (6 with left-sided and 236 with right-sided or bilateral stenosis) and a group of 232 persons without right-sided stenosis, matched by age and sex, were asked to participate in the follow-up study. Two persons with stenosis did not want to participate, 1 died shortly after screening, and 14 did not fulfil the criteria for stenosis/occlusion at the second ultrasound examination and were excluded. Four of the 232 controls had stenosis of the left carotid artery, whereas 1 had stenosis and 1 occlusion of the right carotid artery. These persons are excluded in the calculation of stenosis prevalence, but are included in the stenosis group for the analyses of risk factors. For a few variables (see below), only data on the participants in the follow-up study are available. For most of the analyses, however, all survey participants above the age of 50 years without known stenosis of the carotid arteries (n = 5,514) were used as controls. The cutoff was set at age 50 in order to assure the same range of age among cases and controls.

Ultrasonography

Details about the ultrasound methods and their reproducibility have been published previously [14, 15]. Stenosis of the carotid artery was considered to be present if one or both of the following criteria were met. (1) Peak systolic velocity in tightest stenotic part (PSVs) $\geq$0.2 m/s higher than peak systolic velocity at the point of reference (PSVr), or $\geq$0.1 m/s if the stenosis was located to the bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery (with parallel walls) was used as the point of reference. (2) Thirty-five percent or more reduction in lumen diameter on a longitudinal B-mode scan. Occlusion was diagnosed when an open lumen of the artery was not visible on B-mode or if there was a visible occluding plaque in the artery, and there was no detectable flow in the artery by pulsed Doppler or by color Doppler.

The degree of stenosis was calculated by the following equations: (1) lumen diameter reduction: (plaque thickness/lumen diameter) $\times$100%; (2) cross-sectional lumen area reduction: (plaque area/lumen area) $\times$100%; (3) peak systolic velocity ratio method: (1 – PSVr/PSVs) $\times$100%.

In the following, the three methods will be referred to as the diameter method, the area method and the velocity method. The velocity method was used for calculating the degree of stenosis in those multivariate analyses where this was one of the variables. In the case of bilateral stenosis, the carotid artery with the highest degree of stenosis was selected for analysis of relationship with risk factors.

All measurements were made on-line. Printed images of all measurements were made for later documentation.

Clinical Examination

All participants in the follow-up study underwent interview, clinical neurological and ultrasound examinations of both carotid and vertebral arteries, all performed by 2 experienced neurologists (O.J., E.B.M.). The interviews included detailed questions about previous cerebral or ocular ischemic episodes (both transient and permanent), loss of consciousness, coronary heart disease and intermittent claudication of the lower extremities. For the purpose of this paper, the diagnoses of stroke, hypertension, angina pectoris, previous myocardial infarction and diabetes mellitus were based on the self-administered questionnaires. Hypertension was considered present only if the subject reported current use of antihypertensives, regardless of measured blood pressure levels. Diagnoses of transient ischemic attacks (TIA) and intermittent claudication were based on the neurologists' judgement of the clinical history and examination, and were available only for those who participated in the follow-up study (n = 457). The regional ethical committee approved the study.

Table 1. Prevalence of right carotid artery stenosis in men and women[1]: The Tromsø Study

Age years	Examined	Stenosis		Occlusion		Stenosis or occlusion	
		n	prevalence[2]	n	prevalence[2]	n	prevalence[2]
Women							
<50	383	0	–	0	–	0	–
50–59	849	9	1.1 (0.5–1.9)	0	–	9	1.1 (0.5–1.9)
60–69	1,453	31	2.1 (1.5–3.0)	0	–	31	2.1 (1.5–3.0)
≥70	719	51	7.1 (5.4–9.1)	0	–	51	7.1 (5.4–9.1)
Total	3,404	91	2.7 (2.2–3.3)	0	–	91	2.7 (2.2–3.3)
Men							
<50	292	0	–	0	–	0	–
50–59	807	13	1.6 (0.9–2.7)	1	0.1 (0–0.6)	14	1.7 (1.0–2.8)
60–69	1,308	53	4.1 (3.1–5.2)	4	0.3 (0.1–0.7)	57	4.4 (3.3–5.6)
≥70	609	49	8.0 (6.1–10.4)	8	1.3 (0.6–2.5)	57	9.4 (7.2–11.9)
Total	3,016	115	3.8 (3.2–4.5)	13	0.4 (0.2–0.7)	128	4.2 (3.6–5.0)

[1] Based on the number of persons who had right carotid arteries examined at screening.
[2] Numbers are percentages (95% confidence interval).

Statistical Analysis

Differences between age-adjusted means and proportions were tested for significance by analysis of covariance. Multiple linear regression was used to test for trends across categories. Sex-specific logistic regression analyses were performed to assess the relationship between risk factors and carotid stenosis. Stenosis (yes/no) was used as the dependent variable and the risk factors for atherosclerosis as independent variables, first testing each independent variable separately, and then adding to the multivariate model those variables that were statistically significant for one or both sexes. Interaction with sex was examined in a pooled analysis of women and men with stenosis as dependent variable and the following independent variables: risk factor, sex, risk factor·sex. The same procedure was followed when testing whether risk factors were associated with the degree of stenosis. In multiple linear regression, degree of stenosis was used as the dependent variable, and the risk factors that in univariate analysis were significant predictors were used as independent variables. Only stenotic arteries were used in this analysis. Confidence intervals for proportions were calculated by the Epi Info software package [16]. The SAS software package was used for the other statistical analyses [17]. Two-sided p values lower than 0.05 were considered significant.

Results

Prevalence and Predictors of Stenosis

The prevalence of stenosis or occlusion in the right carotid artery, by age and sex, is shown in table 1. The prevalence (95% CI) among men was 3.8% (3.2–4.6%) and among women 2.7% (2.2–3.3%). No stenoses were found among men below 50 years of age or women below 55 years. The prevalence showed a gradual increase by age for both men and women. Overall prevalence was significantly higher among men than among women (p = 0.001).

Among the 225 persons in the stenosis group, 75 (33%) had bilateral stenosis/occlusion. Thirteen had occlusion of the right internal carotid artery and 6 on the left side. The distribution of different degrees of stenosis by sex, as measured by the three different grading methods, is shown in figure 1. The figure also illustrates that the distribution is dependent on the choice of ultrasound method. The degree of stenosis tended to be higher with the use of the area method than with the two other methods. The proportion of stenoses ≥70% ranged from 24.4 to 36.9% in men and from 12.9 to 21.4% in women, depending on the method of measurement. Men tended to have higher degrees of stenosis than women of the same age (data not shown).

Characteristics of the study population are shown in table 2. The mean age of male cases was 67.6 years (range 54–81) and of male controls 63.6 years (range 50–84), and for female cases and controls 67.8 years (range 57–82) and 64.1 years (range 50–84), respectively. Both men and women with stenosis had significantly higher age-adjusted mean levels of cholesterol, fibrinogen and systolic blood pressure, and lower HDL cholesterol levels than controls. Glycosylated hemoglobin levels were higher in the stenosis group for men, but not for women. Both male and

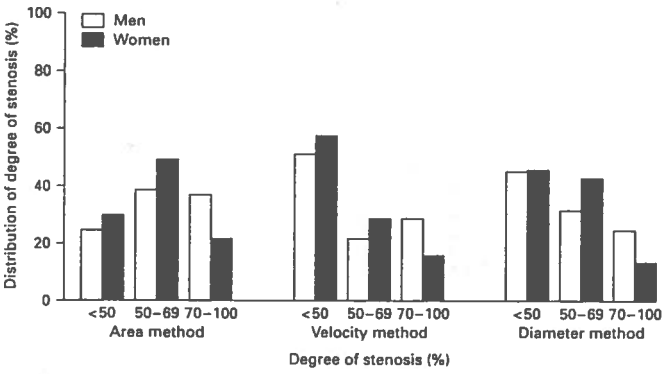

Fig. 1. Distribution of degree of stenosis (<50%, 50–69% and 70–100%) as assessed by three different ultrasound techniques: cross-sectional B-mode scan (area method), longitudinal B-mode scan (diameter method) and velocity measurements (velocity method). Women are represented by black bars, men by open bars.

Table 2. Age-adjusted characteristics of the study population[1]: The Tromsø Study

	Men			Women		
	no stenosis (n = 2,586)	stenosis (n = 132)	p	no stenosis (n = 2,928)	stenosis (n = 93)	p
Age, years	63.6 (5.6)	67.6 (4.9)	0.0001	64.1 (5.6)	67.8 (5.4)	0.0001
Body mass index, kg/cm^2	26.0 (3.4)	26.1 (3.6)	0.7	26.3 (4.5)	26.5 (4.8)	0.6
Waist:hip ratio	0.92 (0.06)	0.93 (0.07)	0.4	0.83 (0.07)	0.83 (0.07)	0.5
Cholesterol, mmol/l	6.54 (1.16)	6.95 (1.17)	0.0001	7.11 (1.26)	7.61 (1.23)	0.0002
HDL cholesterol, mmol/l	1.43 (0.40)	1.35 (0.40)	0.03	1.68 (0.43)	1.57 (0.45)	0.01
Triglycerides, mmol/l	1.75 (1.08)	1.92 (0.98)	0.07	1.63 (0.98)	1.89 (1.06)	0.01
White blood cell count, × 10^9/l	7.0 (1.9)	7.3 (1.9)	0.07	6.7 (1.8)	7.4 (1.9)	0.0006
Fibrinogen, mmol/l	3.4 (0.9)	3.7 (1.0)	0.0001	3.5 (0.8)	3.8 (0.9)	0.0001
Glycosylated hemoglobin, %	5.5 (0.7)	5.7 (1.0)	0.02	5.5 (0.7)	5.5 (0.7)	0.8
Systolic blood pressure, mm Hg	146.6 (20.8)	151.8 (23.5)	0.004	147.8 (23.8)	152.8 (24.3)	0.04
Diastolic blood pressure, mm Hg	85.5 (12.2)	85.5 (13.7)	1.0	82.7 (13.4)	83.1 (14.3)	0.8
Current smoking, %	30.5 (–)	42.5 (–)	0.004	28.9 (–)	41.9 (–)	0.003
Family history of coronary disease, %	54.4 (–)	66.0 (–)	0.03	62.1 (–)	63.8 (–)	0.3

[1] Values are age-adjusted means (SD, unadjusted) or percentages.

female cases had higher mean triglyceride levels and white blood cell count than controls, but for men, these differences were not significant. About 40% of the cases were current smokers, compared to approximately 30% of controls ($p < 0.004$). The odds ratio (95% CI) for stenosis in previous smokers was 1.83 (1.24–2.69, $p = 0.002$), and 2.61 (1.78–3.83, $p = 0.0001$) in current smokers compared to never-smokers. Body mass index and waist-to-hip ratio were similar for cases and controls. In multivariate analysis, age, cholesterol, HDL cholesterol, fibrinogen, systolic blood pressure and current smoking were independent predictors of stenosis in both women and men (table 3), whereas triglycerides, glycosylated hemoglobin and white blood cell count were not. The association between fibrinogen and stenosis was still significant when analysis was limited to nonsmokers ($p = 0.02$). A family history of coronary disease was significantly associated with stenosis in men ($p = 0.03$), but not in women ($p = 0.3$).

Table 3. Multivariate model for risk factors predicting carotid stenosis: The Tromsø Study

	Men			Women		
	odds ratio[1]	95% CI	p	odds ratio[1]	95% CI	p
Age, years	2.05	1.65–2.54	0.0001	1.87	1.44–2.42	0.0001
Cholesterol, mmol/l	1.36	1.13–1.63	0.001	1.51	1.22–1.87	0.0001
HDL cholesterol, mmol/l	0.80	0.65–0.98	0.03	0.78	0.62–0.98	0.03
Fibrinogen, mmol/l	1.28	1.08–1.53	0.005	1.37	1.12–1.67	0.003
Systolic blood pressure, mm Hg	1.21	1.00–1.45	0.04	1.25	1.00–1.57	0.05
Current smoking, yes/no[2]	1.56	1.04–2.35	0.03	2.03	1.25–3.30	0.004
Family history of coronary disease, yes/no[2]	1.55	1.04–2.30	0.03	1.29	0.79–2.09	0.3

[1] For 1 SD increase in independent variable (except for smoking and family history of coronary disease).
[2] Odds for no = 1.

Table 4. Relationship between degree of stenosis[1] and adjusted cardiovascular risk factor levels: The Tromsø Study

	No stenosis (n = 5,514)	Stenosis <50% (n = 119)	Stenosis 50–69% (n = 55)	Stenosis 70–100% (n = 51)	p for equality	p for trend
Age, years	63.9	67.6	69.0	69.3	0.0001	0.0001
Male, %	46.9	59.5	52.7	69.0	0.0002	0.0001
Body mass index, kg/m^2	26.2	26.2	26.1	26.5	0.9	0.6
Cholesterol, mmol/l	6.84	7.33	7.30	7.11	0.0001	0.0001
HDL cholesterol, mmol/l	1.56	1.50	1.49	1.37	0.002	0.0001
Triglycerides, mmol/l	1.69	1.84	1.89	1.96	0.05	0.007
White blood cell count, × 10^9/l	6.9	7.0	7.6	7.7	0.0004	0.0001
Fibrinogen, mmol/l	3.4	3.6	4.0	4.1	0.0001	0.0001
Glycosylated hemoglobin, %	5.5	5.6	5.6	5.6	0.4	0.06
Systolic blood pressure, mm Hg	147.2	149.4	153.2	157.6	0.0009	0.0001
Diastolic blood pressure, mm Hg	84.0	84.0	84.0	84.4	1.0	1.0
Family history of coronary disease, %	58.4	68.9	59.8	58.5	0.1	0.08
Current smoking, %	29.5	34.7	58.9	46.6	0.0001	0.0001

Numbers are means or percentages. Age is adjusted for sex, sex is adjusted for age, and the rest of the variables are adjusted for age and sex. Means were adjusted by ANCOVA, percentages by the direct method for standardization.
[1] The degree of stenosis was estimated by the velocity method.

Table 4 shows age- and sex-adjusted levels of risk factors by degree of stenosis. For age, male gender, cholesterol, HDL cholesterol, triglycerides, white blood cell count, fibrinogen, systolic blood pressure and smoking there was a significant linear trend, indicating a dose-response relationship between these variables and carotid stenosis. There was no gender difference in risk factor associations with stenosis when testing for interaction.

A history of cardiovascular disease, defined as previous or current angina pectoris, myocardial infarction, claudication of the lower extremities, stroke or TIA, was more prevalent among cases than controls (table 5). There was a significant association between reported cerebrovascular events and the degree of carotid stenosis; the odds ratio for having had a cerebrovascular event was 1.26 (95% CI 1.10–1.45) for a 10% increase in degree of stenosis. More cases than controls were using antihyper-

Table 5. Age-adjusted prevalence of symptoms/diseases in the study population: The Tromsø Study

	Men			Women		
	no stenosis	stenosis	p[1]	no stenosis	stenosis	p[1]
Cardiovascular disease	27.8	61.8	0.001	15.5	39.0	0.001
Stroke	3.4	9.1	0.08	2.5	6.6	0.002
TIA[2]	3.9	13.6	0.005	3.3	8.7	0.1
Angina pectoris	11.9	34.4	0.001	8.4	17.5	0.001
Myocardial infarction	10.2	17.3	0.02	3.5	11.5	0.008
Claudication of the lower extremities[2]	7.7	31.0	0.001	1.1	14.0	0.001
Hypertension (treated)	14.8	40.1	0.001	14.9	34.4	0.001
Migraine	6.2	12.8	0.3	23.5	13.3	0.08
Arrhythmia	20.3	28.4	0.2	29.8	32.3	0.9
Cholesterol-lowering treatment[3]	3.0	12.2	0.003	3.0	17.9	0.001
Diabetes mellitus	3.7	3.5	0.6	3.6	3.0	0.8

Numbers are percentages.
1 p values for differences between groups (ANCOVA).
2 Data available only for participants in the follow-up study (n = 446).
3 Data available only for 3,767 persons.

tensive and cholesterol-lowering treatment. Cases had suffered significantly more strokes than controls, and TIA was more prevalent among male cases than among controls. The prevalence of migraine, arrythmia or diabetes mellitus did not differ significantly among cases and controls.

Discussion

The present population-based study is large, includes both women and men, has a high participation rate, and covers a broad age span, all factors that should contribute to reliable estimates of ultrasound-detected carotid artery stenosis in a general population. Previously reported estimates of prevalence of carotid stenosis vary to a great extent. Estimates of prevalence are dependent on how the diagnosis of carotid stenosis is made. Any reduction of lumen can be defined as a stenosis, but a stenosis of 5% is hardly relevant in the clinical setting. In the present study, we wanted the cut-off to be at the level where hemodynamic changes are seen. We chose a combination of velocity and diameter measurements to define stenosis. Hemodynamic changes are usually seen when the lumen diameter is reduced by 35–40% [18–20]. However, since the lumen in the carotid bifurcation and internal bulb often is wider than in the distal internal artery, a substantial reduction of lumen diameter may not necessarily lead to increased velocity in the stenotic part compared to the point of reference. This is why we used a lumen diameter reduction of ≥ 35% as a second criterion of stenosis.

Overall prevalence of right-sided carotid artery stenosis in the present study population was 3.8% among men and 2.7% among women. Given that the prevalences of right-sided and left-sided stenosis are similar [21], and that bilateral stenosis was seen in approximately 30%, this would give an estimated prevalence of 5.3% in men and 3.8% in women for carotid stenosis. These estimates of prevalence of stenosis seem to be quite similar to findings in other comparable studies. However, methods by which carotid stenosis is measured or when a plaque is defined as a stenotic plaque, vary greatly among investigators. Some authors have used diameter reduction alone [4, 6, 7], others a combination of diameter and velocity measurements [8, 10], and one study used lumen reduction in cross-sectional scans [9].

We found a strong independent association between fibrinogen and carotid stenosis. Population-based studies on carotid stenosis have shown different results with regard to fibrinogen; in 2 studies there was no significant association with stenosis [6, 22], in one study fibrinogen was found to be an independent risk factor [5], and another study found a significant relationship between fibrinogen and stenosis only in persons ≥ 65 years of age [8]. In previous prospective studies, fibrinogen has been found to be a predictor of cardiovascular disease [23]. Fibrino-

gen may promote atherosclerosis in different ways, it is involved in the early stages of plaque formation by binding LDL cholesterol and stimulating smooth muscle cell proliferation and migration. It also plays a central role in hemostasis, and thus favors thrombosis, and is linked to inflammation as an acute-phase reactant [24].

In the present study, total cholesterol, HDL cholesterol and triglyceride levels were significantly associated with stenosis in univariate analysis, whereas triglycerides lost their significance in multivariate analysis. Both total and HDL cholesterol (inversely) are recognized as major risk factors for atherosclerosis and cardiovascular disease, whereas the role of triglycerides is less clear. Triglyceride level was a significant predictor of stenosis in both men and women in the Cardiovascular Health Study [10], but in the Framingham study, it was related to degree of stenosis only in women [22]. The results of multivariate statistical analyses including both triglycerides and HDL cholesterol may be difficult to interpret, due to the metabolic interrelationship between HDL and triglyceride-rich lipoproteins. Furthermore, the larger variability of triglyceride levels may result in an underestimation of the relationships between triglycerides and disease [25]. Measurements of fasting triglyceride levels can lower some of this variability, but people are in a nonfasting state most of their time, so fasting levels may not measure their exposure to triglycerides correctly. Nonfasting triglyceride levels have previously been found to be an independent predictor of mortality from coronary heart disease, cardiovascular disease and any-cause mortality among middle-aged Norwegian women [26]. Variability in triglycerides can partly be corrected for by adjusting for time since last meal, although this did not affect the results in the present study.

The study clearly demonstrates that the presence of carotid stenosis is associated with arteriosclerosis in other arterial territories, which is in accordance with previous studies [27–29]. Although diabetes mellitus is associated with a higher prevalence of stroke [30], there was no association between carotid artery stenosis and diabetes mellitus in the present study. Previous reports have found increased intima-media thickness in diabetes [31, 32], supporting the view that excess cerebral ischemic episodes in diabetics are mainly due to microangiopathy.

In conclusion, the prevalence of carotid stenosis in the general population, as measured by ultrasound, is low. It is higher in men than in women and increases with age. Prevalence estimates are dependent on which diagnostic ultrasound method is used. Age, male gender, smoking, total cholesterol, HDL cholesterol (inverse), fibrinogen, systolic blood pressure and a family history of coronary disease are all independent predictors of carotid stenosis.

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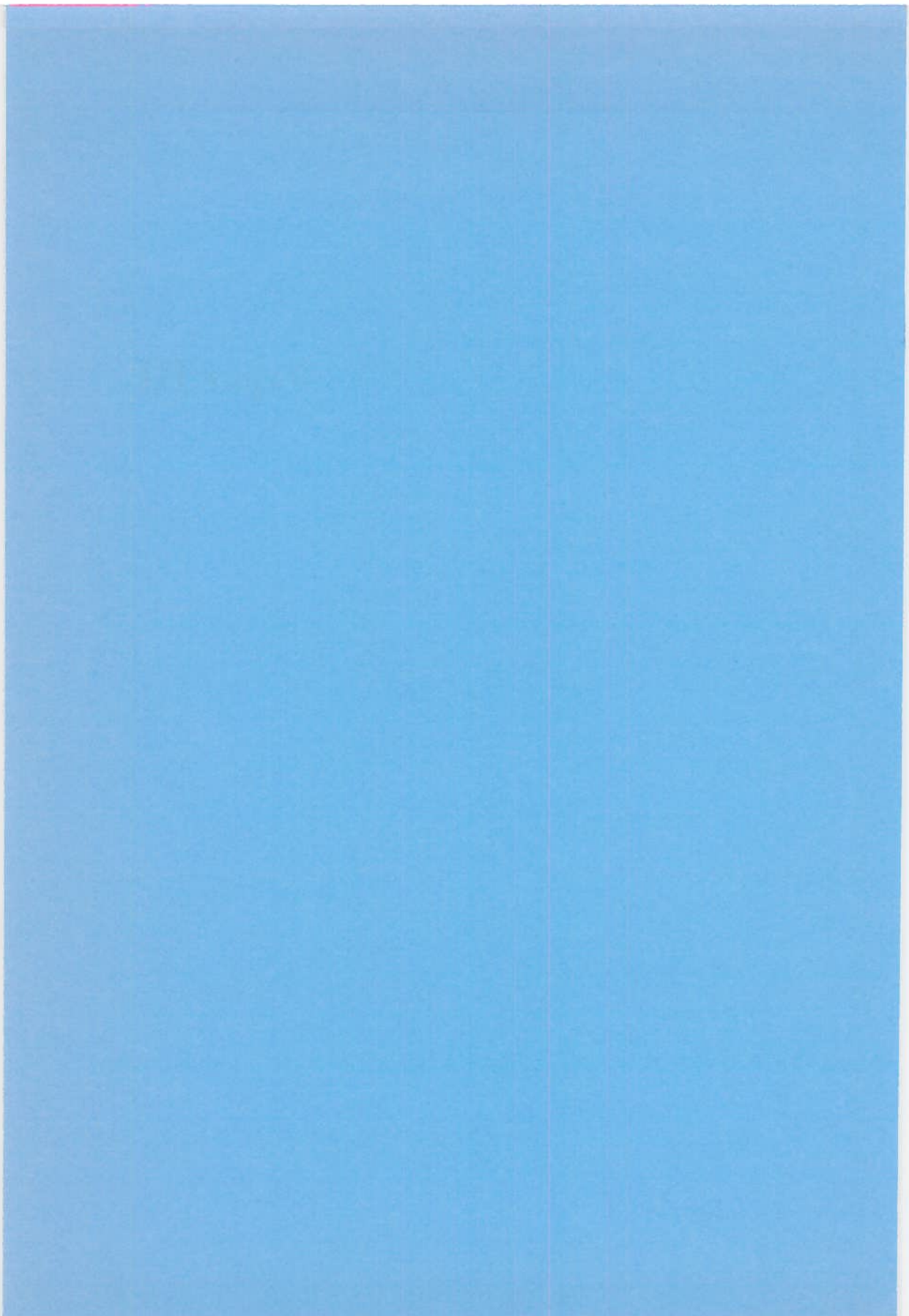
Paper III



Low Levels of High-Density Lipoprotein Cholesterol Are Associated With Echolucent Carotid Artery Plaques. The Tromsø Study

Short title: Association between plaque morphology and HDL cholesterol

Authors: Ellisiv B. Mathiesen, MD; Kaare H. Bønaa, MD, PhD; Oddmund Joakimsen, MD, PhD.

From: The Institute of Community Medicine, University of Tromsø, Norway

Abstract:

Background and Purpose: Ultrasound-assessed plaque morphology is an independent predictor of ischemic stroke. The purpose of this population-based cross-sectional nested case-control study was to examine the risk factors associated with carotid plaque morphology.

Methods: Ultrasonography of the right carotid artery was conducted on 6727 participants in a population health survey (response rate 79%). Plaque echogenicity, defined as reflectance of the emitted ultrasound signal, was scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. Information on cardiovascular risk factors in all 216 participants who had carotid stenosis and in 223 control subjects matched by age and sex who did not have carotid stenosis, was obtained from measurements of blood pressure, weight, height, and non-fasting blood samples, and from a self-administered questionnaire.

Results: In both univariate and multivariate analysis, low levels of high-density lipoprotein (HDL) cholesterol, and increasing degree of stenosis were independently associated with increased risk of having an echolucent plaque. For one standard deviation increase in HDL cholesterol, the adjusted odds of being in a lower plaque echogenicity category, decreased by about 30% (odds ratio 0.69, 95% confidence interval, 0.52-0.93).

Conclusions: These findings indicate that low levels of HDL cholesterol are associated with increased risk of having echolucent, rupture-prone atherosclerotic plaques.

Key words: atherosclerosis • carotid stenosis • lipoproteins, HDL cholesterol • ultrasonography

Lately, there has been an increasing awareness on the importance of the composition of the atherosclerotic carotid plaque as a major risk factor for stroke. From the study of coronary heart disease, it is known that plaques consisting of a lipid-rich core covered by a thin fibrous cap seem to be more rupture-prone and likely to cause clinical events.[1; 2] Plaque echogenicity as assessed by B-mode ultrasound has been found to reliably predict the content of soft tissue and the amount of calcification in carotid plaques.[3-7] Plaques which appear echolucent on B-mode ultrasound, are lipid-rich, whereas echogenic plaques have a higher content of dense fibrous tissue and calcification. Several cross-sectional studies have reported an association between echolucent or hypoechoic plaques and a history of transient ischemic attacks (TIA) and stroke. Recently, we found in a prospective population-based study that plaque morphology was an independent predictor of ischemic cerebrovascular events,[8] and others have reported similar results.[9; 10]

Since plaque morphology can predict future clinical events, it is important to study the risk factors associated with atherosclerotic plaque morphology. Little is known about this, and population-based data are not available. In a study on symptomatic patients with carotid stenosis, echolucent plaques were associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins.[11] The purpose of this study was to assess risk factors associated with carotid artery plaque morphology within the setting of a population-based study.

Methods

Subjects

In 1994-95 all inhabitants aged 25 years and above and living in the municipality of Tromsø, were invited to the fourth survey of the Tromsø Study; a prospective, population-based study on cardiovascular and other chronic diseases.[12] The fourth survey consisted of two screening visits 4 to 12 weeks apart. All subjects between 55-74 years, random 5% samples of subjects in the other age groups, and a selected group of 308 high-risk men aged 40-54 years who had previously taken part in a dietary intervention trial, were invited to the sesond screening visit, which included ultrasonography of the right carotid artery. A total of 6889 subjects attended, 79% of the eligible population. Ultrasonography of the right carotid artery in the neck was performed on 6727 persons; among these, both the right and left carotid artery were examined in 784 persons. The selected group of high-risk men was excluded for

the purpose of this paper. All 242 persons with suspected stenosis and/or occlusion of one or both internal carotid arteries and a control group of 229 persons without right-sided stenosis/occlusion, matched by age and sex, were invited to participate in a follow-up study which included repeat ultrasonography of both the left and right carotid arteries. Among the 242 subjects with suspected stenosis, two persons did not want to participate in the follow-up study, 1 died shortly after the survey, and 14 persons did not fulfil the criteria for stenosis at the repeat ultrasound. They were excluded from the present analyses, as were nine persons with occlusion of the carotid artery since we could not reliably assess plaque morphology in occluded arteries. Four of the 229 controls had stenosis of the left carotid artery, one had stenosis and one had occlusion of the right carotid artery, and were excluded. Thus, a total number of 216 subjects with stenosis and 223 subjects without stenosis were included in the study. Informed consent was obtained from the participants, and the regional ethical committee approved the study.

Ultrasonography

Details about the ultrasound methods and their reproducibility have been published previously.[13,14] The ultrasound assessments both at screening and at the second visit were made by sonographers who were blinded to the laboratory data and data from the questionnaires. Plaque morphology in terms of echogenicity was graded from 1 to 4 as echolucent, predominantly echolucent, predominantly echogenic or echogenic (Figure 1). The vessel lumen was used as the reference structure for defining echolucency, and the bright echo-zone produced by the media-adventitia interface in the far wall was used as the reference structure for defining echogenicity. The reproducibility of the assessment of plaque echogenicity was tested by the use of the kappa statistic, which gave a simple kappa value of 0.56 (95% confidence interval [CI] 0.38-0.74).[14] The weighted kappa value was 0.65 (95% CI 0.51-0.79), which can be characterized as substantial. Stenosis of the carotid artery was considered to be present if one or both of the following criteria were met: 1) Peak systolic velocity in tightest stenotic part (PSVs) $\geq$ 0.2 m/sec higher than peak systolic velocity at the point of reference (PSVr), or $\geq$ 0.1 m/sec if the stenosis was located to the bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery (with parallel walls) was used as the point of reference. 2) Thirty-five % or more reduction in lumen diameter on a longitudinal B-mode

scan. According to these criteria, 119 persons had 35-49% degree of stenosis, and 97 had 50-99% stenosis. Occlusion was diagnosed when an open lumen of the artery was not visible on B-mode or if there was a visible occluding plaque in the artery, and there was no detectable flow in the artery by pulsed Doppler or by color-Doppler. For the purpose of this paper, the degree of stenosis was calculated by the following equation: (1 – PSVr/PSVs) x 100 %, where PSVr denotes peak systolic velocity at the point of reference and PSVs the peak systolic velocity in the stenosis. One subject had missing data on PSVr and another on PSVs. In these persons, the degree of stenosis was estimated by the calculating lumen diameter reduction: (plaque thickness/lumen diameter) x 100 %. In the case of bilateral stenosis, which was present in 29%, the carotid artery with the highest degree of stenosis was selected. All measurements were made on-line and printed images were made for later documentation.

Cardiovascular Risk Factors

Two self-administered questionnaires, checked by trained nurses, comprised information about smoking habits, previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (all yes/no), treated hypertension (never/previous/current), and use of drugs.

Height and weight were measured in light clothing without shoes; body mass index (BMI) was calculated as weight per squared height (kg/m^2). Blood pressure was recorded by the use of an automatic device (Dinamap Vital Signs Monitor) in a separate, quiet room by a specially trained nurse. After the participants had been seated for 2 minutes, three recordings were made at 2-minute intervals. The mean of the two last values is used in this report. Fibrinogen was measured using the PT-Fibrinogen reagent (Instrumentation Laboratory, Italy). White blood cell count was measured by the Coulter method on a Coulter Counter S-Plus STKR analyser (Coulter Electronics Ltd., Luton, U.K.). Serum HDL cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer-Mannheim). Blood pressure and non-fasting blood lipids were measured both at the first and the second screening visit. Participants who at the first visit of the survey had blood pressure or lipid levels above certain limits, were informed about

this. It is possible that some of them received medical advice in the time between the first and the second visit which may have altered their risk factor levels. Because of this, measurements from the first visit were used in all analyses. All blood analyses were performed at the Department of Clinical Chemistry, University Hospital of Tromsø.

Statistical Analysis

Differences between means were tested for statistical significance by the Student's t-test or by analysis of variance, and differences between proportions by χ^2-tests. Linear trend was tested by multiple regression analysis and by a χ^2-test for trend. We performed pooled analyses of women and men since the results were similar in women and men. Logarithmically transformed values of triglycerides were used to approximate normal distribution, and adjustments for time since last meal were made, but since this had virtually no impact on results, untransformed and unadjusted values were used. The independent relationship between risk factors and plaque morphology was tested by logistic regression analysis (cumulative ordinal logit model), where plaque morphology (four categories coded as 1=echolucent plaque, 2=predominantly echolucent, 3=predominantly echogenic, and 4=echogenic plaque) was treated as the dependent variable, and risk factors as independent variables. The model calculates the odds ratio for being in a lower (i.e. more echolucent) category of the dependent variable. A score test confirmed that the proportional odds assumption was met (χ^2 score test = 14.4, 12 degrees of freedom, p = 0.27). Only variables that were statistically significant in univariate analysis were included in the multivariate model, along with age and sex. Interaction with age and sex was examined with plaque morphology as the dependent variable and the following independent variables: risk factor, age (or sex), risk factor*age (or sex). Confidence intervals for proportions and χ^2 for trend in proportions were calculated by the Epi Info software package (Epi Info, version 6.04, 1997). The SAS software package was used for the other statistical analyses (SAS®, release 6.12, 1996). Two-sided p values < 0.05 were considered significant.

Results

Subjects with carotid stenosis had significantly higher mean levels of cholesterol, triglycerides, fibrinogen, white blood cell count and systolic blood pressure, and were more likely to smoke than controls (Table 1). HDL cholesterol

was lower in cases than controls, but the difference was not statistically significant. Age, sex distribution, body mass index and diastolic blood pressure were similar for cases and controls.

Low echogenicity (echolucency) was associated with significantly lower levels of HDL cholesterol, and higher levels of triglycerides and systolic blood pressure (Table 2). The proportion of subjects with echolucent and predominantly echolucent plaques was 69% in the lowest tertile of HDL cholesterol (< 1.23 mmol/L), 58% in the middel tertile (1.23-1.58 mmol/L), and 48% in the highest tertile (≥ 1.59 mmol/L) (p for trend = 0.009, Figure 2). Echolucent plaques tended to be more stenotic than echogenic plaques. There was no significant association between plaque echogenicity and age or the levels of total cholesterol, diastolic blood pressure, fibrinogen, white blood cell count, body mass index, or smoking habits (Table 2), and also no significant association between plaque echogenicity and current treatment of hypertension, or a history of myocardial infarction, angina pectoris, diabetes mellitus or stroke (Table 2). The age-adjusted proportion of echolucent plaques was twice as high in men as in women (7.0% and 3.2%, respectively), but the difference was not statistically significant (p = 0.2).

Low levels of HDL cholesterol were associated with increased risk of plaque echolucency, also when controlling for systolic blood pressure and the degree of stenosis (Table 3). For one standard deviation (SD) increase in HDL cholesterol, the odds of being in a lower plaque echogenicity category decreased by about 30%. There was no interaction between HDL and sex or age. Systolic blood pressure, degree of stenosis and age (inverse) were also associated with plaque echolucency in the multivariate model. Triglyceride levels were not associated with plaque morphology when controlling for the other risk factors (Table 3). We also tested whether the mean values of triglycerides and of HDL measured at the first and second visit performed differently than single measurements. In multivariate analysis with HDL, triglycerides, age, sex, degree of stenosis and systolic blood pressure as covariates, the OR for lower plaque echogenicity by one SD increase in triglycerides was 1.18 (95% CI, 0.88-1.59), and for one SD increase in HDL the OR was 0.72 (95% CI, 0.53-0.97). Thus, the results were essentially the same. Thirteen subjects were using cholesterol-lowering medication. Exclusion of these subjects did not change the results.

In 162 participants, assessment of plaque morphology in the plaque with the highest degree of stenosis was also done at the screening examination, and we were therefore able to examine the reproducibility of the findings. By using screening data, we found in multivariate analysis that an increase in HDL cholesterol by one SD gave an OR of 0.64 (95% CI, 0.44-0.92; p=0.017) for having an echolucent plaque, i.e. essentially the same result as when we used data obtained at the second ultrasound examination (Table 3). When using data from the screening, we found no significant association between plaque echogenicity and systolic blood pressure (OR=0.93, 95% CI, 0.67-1.30).

Discussion

Previously, in a follow-up study on the same participants as in the present study, we found a higher risk for future ischemic cerebrovascular events in subjects with echolucent plaques.[8] Information on the determinants of plaque morphology may help target interventions to stabilize the plaque so it becomes less likely to rupture. This population-based study showed that subjects with echolucent plaques had significantly lower HDL cholesterol, more severe stenosis, higher systolic blood pressure levels, and were younger than subjects with high plaque echogenicity. Studies which compared the relationship between ultrasound plaque echogenicity and histological content of plaques have found that echolucent plaques are typically lipid-rich, whereas echogenic plaques contain more fibrous tissue and are often calcified, confirming the validity of the ultrasound method.[3-7] The reproducibility of the method is acceptable.[11; 13-15]

This is the first study to show an association between HDL cholesterol and plaque morphology. A smaller study of selected symptomatic patients with carotid stenosis found that echolucent plaques were associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins, but not with levels of HDL cholesterol.[11]

There is a strong inverse association between HDL cholesterol and risk of coronary heart disease.[16; 17] An inverse relationship between HDL cholesterol and cerebrovascular disease has also been demonstrated, as well as between HDL cholesterol and carotid atherosclerosis,[18] although the results are not as consistent as for coronary heart disease. The exact mechanism of the protective effect of HDL has been a subject of debate. High-density lipoprotein plays a central role in the removal of cholesterol from cells, and one theory postulates that

HDL has a direct antiatherogenic effect by reversing cholesterol transport from the peripheral tissues to the liver.[19] Direct visualization of lipid transport by HDL in perfused arteries has recently been demonstrated.[20] Another theory emphasises the strong inverse relationship between HDL cholesterol and triglycerides, and suggests that HDL has no direct effect of its own, but acts as a metabolic marker of triglyceride-rich lipoproteins.[21] The present study could be interpreted in favor of the first theory, since the relationship between HDL cholesterol and plaque morphology remained significant when adjusted for triglyceride levels. However, the results of multivariate statistical analyses including both triglycerides and HDL cholesterol may be difficult to interpret due to the metabolic inter-relationship between HDL and triglyceride-rich lipoproteins.[22] Furthermore, the larger variability of triglyceride levels may result in an underestimation of the relationships between triglycerides and disease.[23] Measurements of fasting triglyceride levels can lower some of this variability, but people are in a non-fasting state most of their time so fasting levels may not measure their average exposure to triglycerides correctly.[24] Variability in triglycerides can partly be corrected for by adjusting for time since last meal, although this did not affect the results in the present study. The large variability can also partly be compensated for by repeated measurements, however, the results were essentially the same when mean values of triglycerides and of HDL cholesterol measured at the first and second visit were used.

We also observed that high levels of systolic blood pressure were associated with more echolucent carotid plaques, however, the association is uncertain since it could not be reproduced when the echogenicity scores obtained at the screening examination were used. Atherosclerosis is a pressure-dependent disease since it develops only in vessels exposed to arterial pressures. High blood pressure may increase the development of lipid-rich atherosclerotic plaques since low-density lipoproteins may enter the intima of the arterial wall by pressure-driven convection.[25] Hypertension is a well established risk factor for both atherosclerosis and stroke.[26; 27] Thus, it is not surprising that systolic blood pressure was related to a plaque type that is more likely to cause clinical events. However, our results are in conflict with those reported by Sillesen et al.,[6] who found that patients with arterial hypertension had less soft tissue in their plaques than normotensive patients. This issue needs

further examination in future, preferably prospective studies.

The association between plaque echolucency and more advanced stenosis seems to add evidence to the assumption that certain plaque types are more prone to progression than others. The present data suggest that echolucent plaques are more likely than fibrous and/or calcified plaques to develop into advanced stenoses, although the sequence of events can not be determined in a cross-sectional study. Both thrombi and hemorrhage appear as echolucent structures. Thrombi may be more likely to occur in high-grade stenosis, and intraplaque hemorrhage has been found more frequent in high-grade stenosis.[28] However, hemorrhage seldom occupies more than 2% of total plaque size,[29] thus, it seems unlikely that hemorrhage contributes substantially to the relationship between plaque echogenicity and severity of stenosis. Our findings are in line with previous studies, which found that the proportion of echolucent plaques was increased in high-grade stenosis.[9]

In a previous study,[30] we observed that men had significantly higher percentage of echolucent plaques than women. This was also found in the present study, but the difference between women and men was not significant, due to the lower number of participants. Our studies suggest that part of the gender difference in cardiovascular disease may be associated with gender differences in plaque morphology. Women have higher HDL cholesterol levels than men from puberty and throughout old age,[31] and may therefore be less likely than men to develop echolucent, rupture-prone atherosclerotic plaques.

There are some limitation to this study. The number of subjects in each plaque echogenicity group is low, and this may have limited the statistical power of the analyses. Although reproducibility on plaque echogenicity was good, some misclassification probably occurred. Computerized quantification of plaque morphology could probably improve the ultrasound assessment of plaque morphology.[32; 33] We may also assume that there were some misclassification of the degree of stenosis, however, the interobserver agreement on the grading of stenosis in the present study has been found acceptable,[14] and the method has been validated in previous studies.[34; 35] Any misclassification both with respect to the risk factors and plaque echogenicity would most likely lead to underestimation of the true relationship between them.[36]

On the basis of the present population-based observational data, we hypothesize that high density lipoprotein

contributes in the development of echolucent atherosclerotic plaques. However, since we used a cross-sectional study design, this hypothesis requires further investigation in experimental studies.

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TABLE 1: Characteristics of Participants With and Without Carotid Stenosis: The Tromsø Study

	Carotid Stenosis		
	Yes (n=216)	No (n=223)	*P* *
Male sex, %	56.9	59.6	0.6
Age, years	68.2 (5.6)	67.7 (5.8)	0.4
Body mass index, kg/m²	26.2 (4.1)	25.8 (3.7)	0.2
Total cholesterol, mmol/L	7.27 (1.28)	6.86 (1.20)	0.0006
HDL cholesterol, mmol/L	1.46 (0.42)	1.52 (0.42)	0.08
Triglycerides, mmol/L	1.91 (1.00)	1.61 (0.82)	0.0007
Fibrinogen, mmol/L	3.8 (1.0)	3.6 (0.9)	0.002
White blood cell count, E.09/L	7.3 (1.9)	6.6 (1.8)	0.0002
Systolic blood pressure, mm Hg	156.6 (24.3)	149.1 (22.2)	0.0008
Diastolic blood pressure, mm Hg	85.3 (14.2)	84.5(12.5)	0.5
Current smoking, %	38.4	25.1	0.003

Numbers are means (standard deviations) or percentages.

*Student's *t* test was used for comparison of mean values and χ^2-test was used for comparison of proportions.

TABLE 2. Risk Factor Levels in Subjects With Stenotic Plaques Stratified According to Plaque Echogenicity: The Tromsø Study

	Plaque Echogenicity				*P* for Trend	
	Echolucent (n=25)	Predominantly Echolucent (n=101)	Predominantly Echogenic (n=69)	Echogenic (n=21)	For Equality*	For Linear Trend†
Male sex	72.0 (18)	56.4 (57)	55.1 (38)	47.6 (10)	0.4	0.1‡
Age, years	67.4 (6.0)	68.0 (5.8)	68.8 (5.4)	68.7 (4.2)	0.2	0.2
Body mass index, kg/m²	26.0 (4.3)	26.8 (3.8)	26.1 (4.7)	24.7 (3.3)	0.2	0.2
Cholesterol, mmol/L	7.47 (1.49)	7.29 (1.22)	7.23 (1.24)	7.13 (1.48)	0.9	0.4
HDL cholesterol, mmol/L	1.38 (0.38)	1.38 (0.39)	1.49 (0.41)	1.78 (0.53)	0.0007	0.0004
Triglycerides, mmol/L	1.94 (1.11)	2.09 (1.04)	1.83 (0.91)	1.26 (0.65)	0.005	0.005
Fibrinogen, mmol/L	4.1 (1.1)	3.8 (0.9)	3.9 (1.0)	3.7 (0.8)	0.6	0.7
White blood cell count, E.09/L	7.7 (2.0)	7.3 (1.9)	7.2 (1.9)	7.2 (1.7)	0.8	0.4
Systolic blood pressure, mm Hg	167.7 (28.5)	156.4 (24.2)	154.8 (23.9)	150.2	0.07	0.02
Diastolic blood pressure, mmHg	90.6 (17.2)	84.3 (14.4)	85.9 (13.7)	81.9 (9.5)	0.2	0.2
Current smoking	44.0 (11)	38.6 (39)	33.3 (23)	47.6 (10)	0.2	0.9‡
Degree of stenosis, %	56.7 (24.6)	49.3 (22.9)	42.1 (22.6)	43.5 (21.3)	0.03	0.004
Treated hypertension	36.0 (9)	36.6 (37)	29.0 (20)	33.3 (7)	0.8	0.5‡
Angina pectoris	20.0 (5)	31.9 (32)	26.1 (18)	23.8 (5)	0.6	0.6‡
Previous myocardial infarct	4.0 (1)	17.8 (18)	15.9 (11)	19.1 (4)	0.4	0.3‡
Diabetes mellitus	8.0 (2)	4.0 (4)	4.4 (3)	5.0 (1)	0.9	0.7‡
Previous stroke	8.0 (2)	6.9 (7)	7.3 (5)	19.5 (4)	0.3	0.3‡

Numbers are means (SD) or percentages (n). *Analysis of variance.†Multiple linear regression. ‡χ^2 for linear trend

TABLE 3. Cumulative Ordinal Logistic Regression Model for Risk Factors Associated With Plaque Echolucency. The Tromsø Study

	SD	OR*	95% CI	*P*
Age, years	5.6	0.74	0.57–0.97	0.03
Male sex	–	1.27	0.75–2.15	0.4
Degree of stenosis, %	23.2	1.38	1.07–1.80	0.02
HDL cholesterol, mmol/L	0.42	0.69	0.52–0.93	0.01
Triglycerides, mmol/L	1.00	1.17	0.88–1.57	0.3
Systolic blood pressure, mm Hg	24.3	1.35	1.03–1.76	0.03

* The adjusted odds ratio predicts the probability of being in a lower category for one SD increase in the independent variable, except for male gender, where the odds ratio predicts the odds of men being in a lower category compared to the odds of women. Only subjects with stenosis are included in the model.

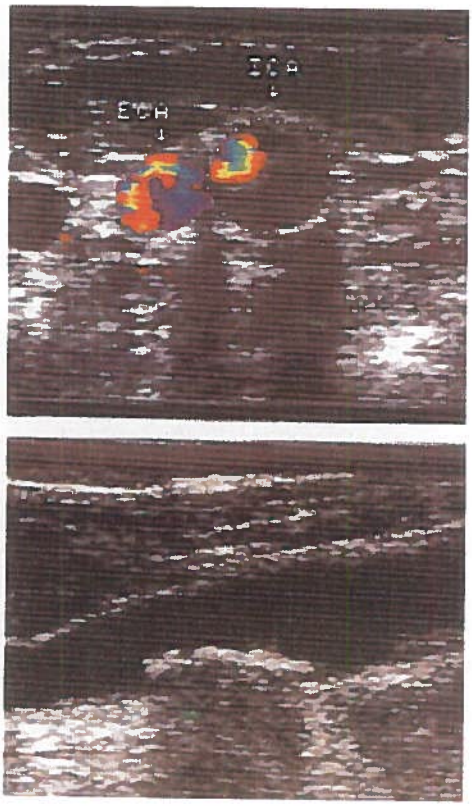
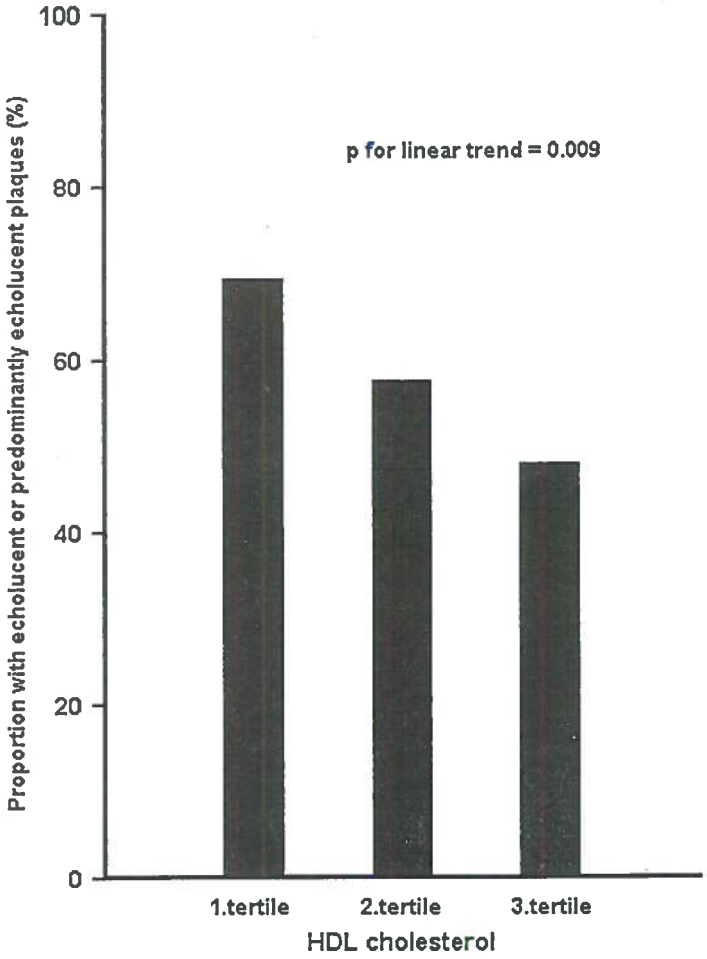


Figure 1. Echolucent and Echogenic Plaques.

Top, Duplex image of an echolucent plaque in the internal carotid artery, shown in the cross-sectional plane. The outline of the original lumen is marked by the dotted line. ICA; internal carotid artery, ECA; external carotid artery.

Bottom, B-mode image of an echogenic plaque with acoustic shadowing in the far wall of the internal carotid artery.

Figure 2. Proportion of subjects with echolucent and predominantly echolucent stenotic plaques in tertiles of HDL cholesterol levels.



Serum HDL cholesterol tertiles were <1.23, 1.23-1.58, and ≥ 1.59 mmol/L.

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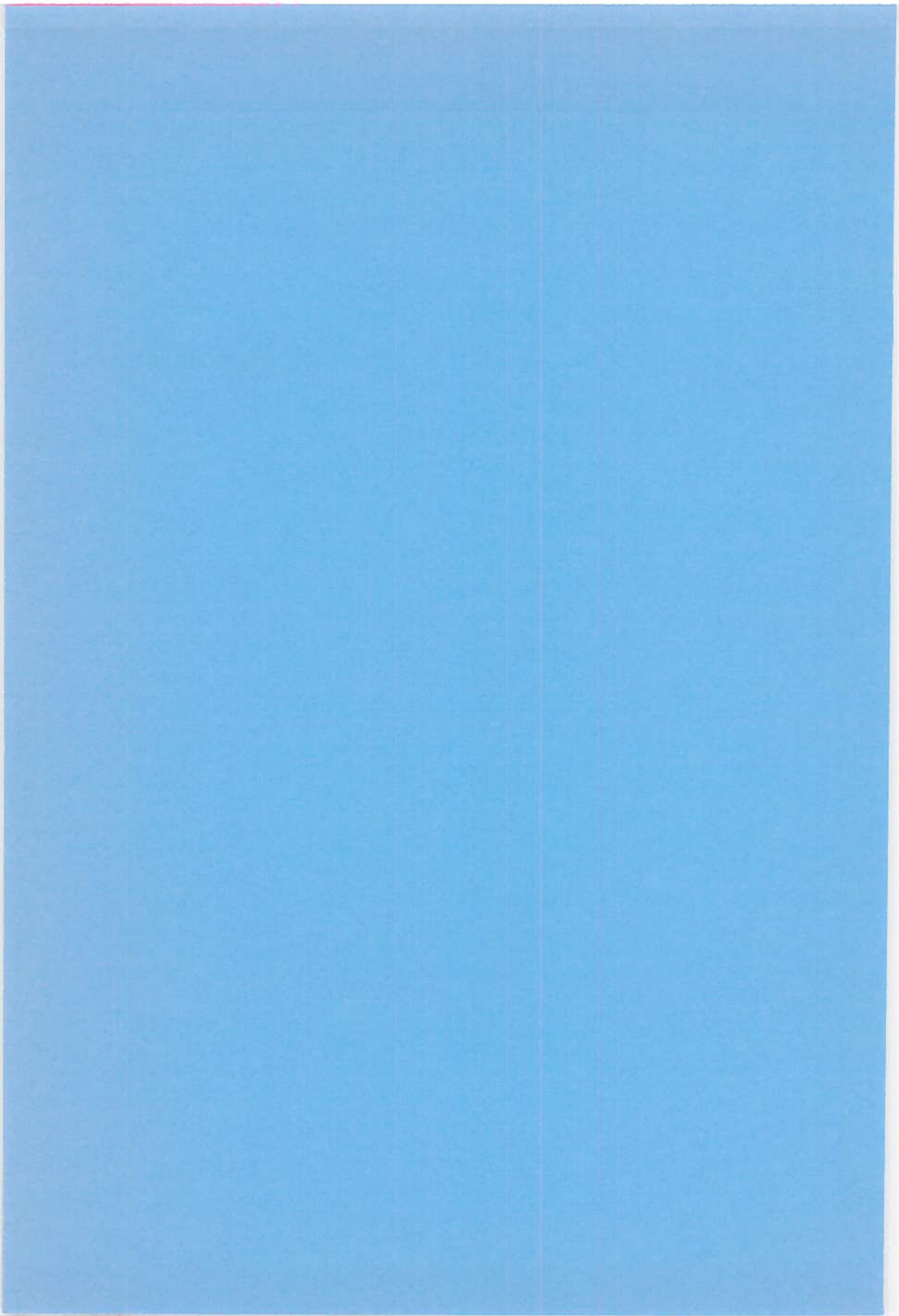

Echolucent Plaques Are Associated With High Risk of Ischemic Cerebrovascular Events in Carotid Stenosis

The Tromsø Study

Ellisiv B. Mathiesen, MD; Kaare H. Bønaa, MD, PhD; Oddmund Joakimsen, MD, PhD

Background—The purpose of the study was to assess in a prospective design whether plaque morphology is associated with risk of ischemic stroke and other cerebrovascular events in subjects with carotid stenosis.

Methods and Results—A total of 223 subjects with carotid stenosis (123 with 35% to 49% degree of stenosis, 100 with 50% to 99% stenosis) and 215 control subjects matched by age and sex who participated in a population health survey at baseline were followed up for 3 years. Plaque echogenicity was assessed by ultrasound at baseline and scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. Forty-four subjects experienced ≥1 ischemic cerebrovascular events in the follow-up period. Plaque echogenicity, degree of stenosis, and white blood cell count were independent predictors of cerebrovascular events. The unadjusted relative risk for cerebrovascular events was 13.0 (95% CI 4.5 to 37.4) in subjects with echolucent plaques and 3.7 (95% CI 0.7 to 18.2) in subjects with echogenic plaques when subjects without stenosis were used as the reference. The adjusted relative risk for cerebrovascular events in subjects with echolucent plaques was 4.6 (95% CI 1.1 to 18.9), and there was a significant linear trend (P=0.015) for higher risk with increasing plaque echolucency. The adjusted relative risk for a 10% increase in the degree of stenosis was 1.2 (95% CI 1.04 to 1.4).

Conclusions—Subjects with echolucent atherosclerotic plaques have increased risk of ischemic cerebrovascular events independent of degree of stenosis and cardiovascular risk factors. Subjects at high risk for ischemic vascular events may be identified by ultrasound assessment of plaque morphology. (*Circulation*. 2001;103:2171-2175.)

Key Words: plaque ■ ultrasonics ■ carotid arteries ■ stenosis ■ stroke ■ follow-up studies

Stroke is the second leading cause of death in the world,[1] with stenotic atheromatous plaques of the carotid bifurcation as one of the important risk factors. The degree of stenosis is recognized as an important risk factor for stroke. It is well known, however, that many high-grade stenoses remain stable and never cause cerebrovascular events, whereas others rapidly produce serious, potentially life-threatening disease. Thus, there has been a search for additional risk factors that might help identify the individuals with a high risk for stroke.

Plaque echogenicity as assessed by B-mode ultrasound has been found to reliably predict the content of soft tissue and the amount of calcification in carotid plaques.[2] Plaques that appear echolucent on B-mode ultrasound are lipid-rich, whereas echogenic plaques have a higher content of fibrous tissue and calcification.[3,4] Plaque echogenicity has been reported to be associated with stroke and other cerebrovascular events in univariate analysis in previous studies.[5–16] Most of these were cross-sectional,[6,7,9,12–15] but an association has also been found in prospective studies.[5,8,10,11,16] Only 2 prospective studies have made adjustments for other cerebrovascular risk factors.[8,16] In a majority of previous studies, the participants were symptomatic patients referred to ultrasonography and/or carotid endarterectomy, whereas little is known about plaque echogenicity and the risk of stroke in the general population of stenotic subjects.

The purpose of the present study was to assess, in a population-based, prospective design, whether plaque morphology is an independent predictor of stroke and other cerebrovascular events.

Methods

In the fourth survey of the Tromsø Study in 1994 to 1995, a total of 6727 persons, 77% of the eligible population, were examined with ultrasound of the carotid arteries, and among these, 237 subjects were found to have stenosis or occlusion of the carotid artery.[17] After 3 years, all subjects with carotid stenosis and 227 control subjects without stenosis, matched by age and sex and recruited from the study population, were invited to a follow-up examination. Ten subjects (2 with stenosis and 8 without) did not want to participate, and 5 subjects (1 with stenosis and 4 without) had moved out of the region and were excluded from the study. Informed consent was obtained from the participants, and the regional ethical committee approved the study.

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From the Institute of Community Medicine, University of Tromsø, Norway.

Correspondence to Ellisiv B. Mathiesen, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway. E-mail ellisiv.mathiesen@ism.uit.no

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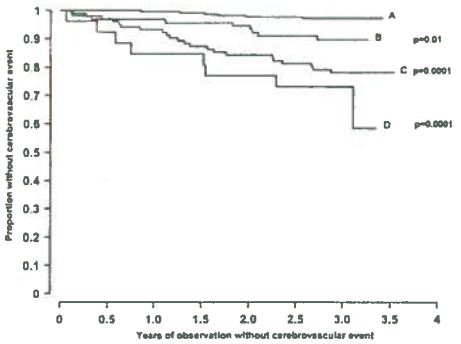
Details about the ultrasound methods have been published previously.[17,18] Briefly, high-resolution B-mode and color Doppler/pulsed-wave Doppler ultrasonography of both carotid arteries were performed with an ultrasound scanner (Acuson Xp10 128 ART) equipped with a linear-array 5- to 7-MHz transducer. Plaque morphology in terms of echogenicity, defined as reflectance of the emitted ultrasound signal, was assessed in a modified version of the classification proposed by Gray-Weale et al[19,20] and graded from 1 to 4 as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. The vessel lumen was used as the reference structure for defining echolucency, and the bright echo zone produced by the media-adventitia interface in the far wall was used as the reference structure for defining echogenicity. We have previously assessed interobserver reproducibility of plaque morphology in stenotic arteries, with acceptable results (κ=0.56, 95% CI 0.38 to 0.74).[18] Subjects with plaques that could not be classified because of either occlusion of the carotid artery (n=10) or too much echo shadowing or unsatisfactory image quality (n=1) were excluded. Plaque morphology was not recorded in 1 subject. Thus, assessment of plaque morphology was available in 226 cases at baseline, but because of nonparticipation in the follow-up study, a total of 223 cases and 215 controls were included in the analyses.

The degree of stenosis was calculated by the following equation: (1−PSVr/PSVs)×100%, where PSVr denotes peak systolic velocity at the point of reference (here, the distal carotid artery) and PSVs the peak systolic velocity in the stenosis. One subject had missing data on PSVr and another on PSVs. In these persons, the degree of stenosis was estimated by calculating lumen diameter reduction: (plaque thickness/lumen diameter)×100%. An increase in PSVs with respect to PSVr, corresponding to ≈35% lumen diameter stenosis,[21] or a narrowing of the lumen diameter in the longitudinal plane by 35% was used as the cutoff point for stenosis. In 55% of the cases, the degree of stenosis was <50%, in 26% of the cases the stenosis was 50% to 69%, and 19% of cases had stenosis ≥70%. In the case of bilateral stenosis or multiple plaques, the carotid artery or plaque with the highest degree of stenosis was selected for analysis.

At the baseline examination, measurements of height, weight, body mass index, blood pressure, nonfasting serum total cholesterol, HDL cholesterol, triglycerides, fibrinogen, and white blood cell count were done, and information about smoking habits was collected from self-administered questionnaires.[17]

During the follow-up period, subjects with a stenosis of ≥70% and incident ipsilateral transient ischemic attacks (TIAs) or nondisabling strokes (n=9) were referred to surgery, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) guidelines.[22] Symptomatic cases with <70% stenosis and asymptomatic subjects with high-grade stenosis were given prophylactic antiplatelet treatment unless contraindicated, usually aspirin 160 mg/d. Endarterectomy was performed on an asymptomatic person with a rapidly progressing stenosis in 1 internal carotid artery (from 40% to 90% in 1 year) and contralateral occlusion and on 2 subjects with asymptomatic high-grade stenosis before renal transplantation. All other participants were given the best medical therapy available to lower cardiovascular risk factor levels.

At the 3-year follow-up examination, a detailed history of cerebrovascular events was recorded, and clinical neurological and ultrasound examinations were done in all subjects. All interviews and examinations were done by the same neurologist (E.B.M.), who was blinded to previous assessments of plaque echogenicity but not to whether the subject had stenosis or not. TIA was defined as a new-onset focal neurological abnormality lasting <24 hours, with no other apparent cause than cerebrovascular, and stroke likewise, except that the duration had to be >24 hours unless interrupted by death.[23] Strokes were considered to be of ischemic origin when cerebral hemorrhage was excluded by CT or MR scans of the brain, which were performed in all subjects with a clinical diagnosis of stroke. Amaurosis fugax was defined as partial or complete uniocular loss of vision of sudden onset lasting <1 hour. Deceased subjects (27 cases and 11 controls) were identified by linkage to the National Population Register. Data on cerebrovascular events and details of all deaths were documented by hospital records (available in all but 2), death certificates (available in all), and autopsy records (available in 11 subjects).



Graph of event-free survival for subjects without stenosis and subjects with stenosis according to plaque echogenicity. A, Subjects without stenosis; B, subjects with echogenic and predominantly echogenic plaques; C, subjects with predominantly echolucent plaques; and D, subjects with echolucent plaques. Probability values refer to comparison between group B, C, or D vs control subjects (A).

Differences in mean values between groups were compared by ANOVA. Differences in proportions were tested by χ^2 test and Fisher's exact test. Significance of trends was tested by linear regression or by χ^2 test for trend. Event rates were calculated by dividing number of events by observation-years. The Kaplan-Meier method was used for survival analysis, with censoring for nonstroke death, carotid endarterectomy, or at the time of the 3-year follow-up examination. Few ischemic events occurred in the echogenic group, and the proportion of survival was similar to the predominantly echogenic group; thus, the predominantly echogenic and echogenic groups were pooled in the life-table analysis (Figure). Cox proportional-hazards regression models were used to model the outcomes stroke and cerebrovascular event as a function of plaque echogenicity, degree of stenosis, and cardiovascular risk factors. Predictor variables were logarithmically transformed to achieve normal distribution when appropriate, but because this had no significant influence on results, untransformed values were used. The SAS software package was used for the statistical analyses (SAS, release 6.12, 1996), except for χ^2 tests for trend, which were calculated by the Epi Info software package (Epi Info, version 6.04, 1997). Two-sided probability values of $P<0.05$ were considered significant.

Results

Selected characteristics of the study population are shown in Table 1. Persons with echolucent plaques had a higher degree of stenosis, lower levels of HDL cholesterol, and higher levels of total cholesterol, fibrinogen, white blood cell count, and systolic blood pressure than others. A larger proportion of subjects with stenosis than subjects without stenosis were current smokers. There was a male preponderance and slightly lower age among subjects with echolucent plaques compared with subjects in the other plaque morphology groups and subjects without stenosis, but these differences were not significant. There were no significant differences in diastolic blood pressure or body mass index between groups.

Compared with subjects with no stenosis, subjects with stenosis had an increased risk for stroke (RR 2.72, 95% CI 1.06 to 7.03) and any cerebrovascular event (6.95, 95% CI

TABLE 1. Risk Factors in Subjects Without and With Carotid Stenosis, Stratified by Plaque Echogenicity: The Tromsø Study

		Stenosis				P†	
	No Stenosis (n=215)	Echogenic (n=21)	Predominantly Echogenic (n=72)	Predominantly Echolucent (n=103)	Echolucent (n=27)	For Equality	For Trend
Male sex*	61.4 (132)	47.6 (10)	56.9 (41)	58.3 (60)	74.1 (20)	0.4	0.2
Age, y	67.5 (6.1)	68.7 (4.2)	68.1 (6.3)	67.6 (6.5)	66.8 (6.9)	0.8	0.2
Degree of stenosis, %	—	43.5 (21.3)	41.9 (22.5)	50.2 (23.2)	57.6 (24.2)	0.008†	0.0001‡
Cholesterol, mmol/L	6.86 (1.21)	7.13 (1.48)	7.25 (1.27)	7.35 (1.23)	7.43 (1.43)	0.005	0.0001
HDL cholesterol, mmol/L	1.54 (0.41)	1.78 (0.53)	1.47 (0.41)	1.39 (0.39)	1.38 (0.36)	0.0004	0.001
Triglycerides, mmol/L	1.58 (0.78)	1.26 (0.65)	1.91 (1.08)	2.07 (1.04)	2.03 (1.16)	0.0001	0.0001
Fibrinogen, mmol/L	3.6 (0.9)	3.7 (0.8)	3.8 (1.0)	3.8 (0.9)	4.1 (1.1)	0.03	0.004
White blood cell count	6.6 (1.8)	7.2 (1.7)	7.2 (1.9)	7.3 (1.8)	7.5 (2.0)	0.008	0.0007
Current smoking*	25.6 (55)	47.6 (10)	31.9 (23)	39.8 (41)	44.4 (12)	0.01	0.003
Body mass index, kg/m²	25.9 (3.8)	24.6 (3.3)	26.4 (4.7)	26.7 (3.9)	25.8 (4.2)	0.2	0.1
Systolic blood pressure, mm Hg	148.8 (22.3)	150.2 (17.3)	155.0 (23.3)	155.7 (24.5)	167.0 (27.8)	0.001	0.0001
Diastolic blood pressure, mm Hg	84.5 (12.3)	81.9 (9.5)	86.5 (13.6)	84.1 (14.4)	90.2 (16.7)	0.2	0.2
History of ischemic cerebrovascular disease*	7.0 (15)	28.6 (6)	13.9 (10)	23.3 [24)	22.2 (6)	0.0002	0.0001

Numbers are unadjusted means (SD) or *percentages (numbers).
†*P* for equality was calculated by ANOVA; *P* for trend was tested by linear regression or χ^2 test for trend.
‡Subjects without stenosis excluded.

2.94 to 16.45). There were trends toward increasing incidence of both TIA and stroke with increasing degree of echolucency (Table 2). For amaurosis fugax, the trend was less clear, because of lack of events in 3 of the groups. Although the absolute number of ipsilateral events was low (n=22), there was a significant linear trend toward higher number of events with increasing echolucency (P=0.017) (Table 2). When adjusted for age, sex, and degree of stenosis, the relative risk of ipsilateral events in the predominantly echolucent group was 3.52 (95% CI 1.0 to 12.42), and in the echolucent group, 3.64 (95% CI 0.79 to 16.75). In this model, the combined group of echogenic and predominantly echogenic plaques was treated as the reference, because there were no incidents in the echogenic group.

There was a significant linear trend toward higher risk for cerebrovascular events with more echolucent plaques (Table 3, Figure). The unadjusted relative risk for cerebrovascular events was >12 times higher in subjects with echolucent plaques than in subjects without stenosis. When adjustments were made for age, sex, and degree of stenosis, there was still a significant linear trend toward higher risk with increasing echolucency (Table 3). The exclusion of persons with previous cerebrovascular events did not alter the results (data not shown). The adjusted relative risk for each 10% increase in degree of stenosis was 1.19 (95% CI 1.04 to 1.37).

White blood cell count, fibrinogen, and smoking were significant predictors of events in univariate analysis, whereas there were no significant associations between risk of cerebrovascular events and age, sex, total cholesterol, HDL cholesterol, triglycerides, systolic or diastolic blood pressure, or body mass index (data not shown). In a multivariate Cox regression in which age, sex, degree of stenosis, fibrinogen,

TABLE 2. Incidence of Cerebrovascular Ischemic Events During a Median of 3.0 Years of Follow-Up in Subjects With No Carotid Stenosis and Subjects With Stenosis, According to Plaque Echogenicity: The Tromsø Study

		Stenosis			
	No Stenosis (n=215)	Echogenic (n=21)	Predominantly Echogenic (n=72)	Predominantly Echolucent (n=103)	Echolucent (n=27)
TIA	0.5 (1)	4.8 (1)	6.9 (5)	9.7 (10)	18.5 (5)
Amaurosis fugax	0	0	4.2 [3)	7.8 (8)	0
Ischemic stroke	2.8 (6)	4.8 (1)	4.2 (3)	7.8 (8)	14.8 (4)
Any cerebrovascular event*	2.8 (6)	9.5 (2)	9.7 (7)	21.4 [22)	29.6 (8)
Any ipsilateral cerebrovascular event†	0	0	5.8 (4)	14.7 (14)	17.4 (4)

Values are percentages (n).
*χ^2 for linear trend 26.9, P = 0.000001.
†χ^2 for linear trend 5.65, P = 0.017.

TABLE 3. Risk of Cerebrovascular Events Among Persons Without and With Carotid Stenosis, Stratified According to Plaque Echogenicity: The Tromsø Study

		Stenosis				
	No Stenosis	Echogenic	Predominantly Echogenic	Predominantly Echolucent	Echolucent	*P* for Linear Trend
Person-years of follow-up	628.38	57.40	186.72	269.95	64.24	
Cerebrovascular events	6	2	7	22	8	
Event rate per 100 person-years	0.95	3.48	3.75	8.15	12.45	
Unadjusted RR (95% CI)	1.00	3.67 (0.74–18.20)	3.94 (1.32–11.71)	8.22 (3.32–20.37)	12.98 (4.50–37.43)	0.0001
Adjusted RR (95% CI)						
Model I	1.00	3.71 (0.75–18.43)	3.92 (1.32–11.68)	8.27 (3.34–20.52)	12.84 (4.44–37.16)	0.0001
Model II	1.00	1.58 (0.27–9.20)	1.72 (0.47–6.32)	3.07 (0.89–10.58)	4.43 (1.11–17.67)	0.015
Model III	1.00	1.84 (0.30–11.23)	2.00 (0.53–7.60)	3.56 (1.02–12.51)	4.56 (1.10–18.93)	0.015

RR indicates relative risk.

Model I was adjusted for age and sex; model II was adjusted for age, sex, and degree of stenosis; and model III was adjusted for age, sex, degree of stenosis, white blood cell count, fibrinogen, smoking, and previous cerebrovascular events.

white blood cell count, smoking, and plaque echogenicity were included in the model, only white blood cell count ($P=0.004$), degree of stenosis ($P=0.019$), and plaque echogenicity ($P=0.026$) were independent predictors of cerebrovascular events. Inclusion in the multivariate model of other cardiovascular risk factors, such as systolic blood pressure and HDL cholesterol, did not change the results.

Discussion

In the present study, subjects with echolucent stenotic plaques had a much higher risk of stroke and cerebrovascular events than subjects with other plaque types. The increased risk was independent of degree of stenosis, age, sex, and other cardiovascular risk factors. Thus, the present study supports the existence of a higher risk of stroke in subjects with echolucent plaques.

It is known from autopsy studies of coronary heart disease that lipid-rich plaques are unstable and prone to rupture and thrombus formation and are associated with unstable angina, myocardial infarction, and sudden death.[24,25] On B-mode ultrasound assessments, lipids, thrombi, and hemorrhage all will appear as echolucent structures. Hemorrhage seldom occupies >2% of total plaque size,[26] however; thus, it seems unlikely that hemorrhage contributes substantially to the observed echolucency. The association between plaque morphology in carotid arteries and cerebrovascular disease in the present prospective study may therefore be analogous to the relationship between lipid-rich plaques and coronary events. Because many clinical ischemic events occurred in a vascular territory different from the one supplied by the artery with the echolucent plaque, however, we cannot assume the same causal relationship between plaque morphology and events as seen in studies of coronary heart disease, although it seems clear that plaque echolucency is a marker of higher risk.

Our results are in line with the findings from previous studies. In the Cardiovascular Health Study (CHS),[16] a cohort of 4886 persons ≥65 years old were followed up for a mean of 3.3 years. Plaque echogenicity was characterized as hypoechoic, isoechoic, or hyperechoic. The relative risk of ipsilateral stroke for hypoechoic plaques was 2.78 (95% CI 1.36 to 5.69). The hypoechoic group probably corresponds to our echolucent group and perhaps partly to the predominantly echolucent group. The older study population probably explains why the stroke rate was higher in the CHS than in the present study. Sterpetti et al[8] examined prospectively 214 consecutive patients referred to a vascular laboratory and found that degree of stenosis ≥50% and heterogeneous plaques were independent predictors of new cerebrovascular events. The term heterogenic in the Sterpetti study referred to plaques with mixed high-, medium-, and low-level echoes and probably included plaques containing zones with echolucency, whereas the term homogenic was used to characterize all plaques that gave uniformly high-level echoes and probably corresponds to what we have called echogenic.

Known cardiovascular risk factors such as sex, blood pressure, total cholesterol, and HDL cholesterol were not significant predictors of cerebrovascular events in the present study. This is not surprising, because these risk factors are associated with both presence of stenosis and plaque echogenicity, which will attenuate the effect of the cardiovascular risk factors on cerebrovascular events. Also, the effects of age will be difficult to detect in a matched design. Smoking, fibrinogen, and white blood cell count were the only risk factors that were significant predictors of events in univariate analysis. Both fibrinogen and leukocyte count correlate with smoking. Interestingly, in multivariate analysis, only white blood cell count was a significant predictor of cerebrovascular events (along with degree of stenosis and plaque echolucency). This might reflect inflammatory processes related to the atherosclerotic lesion.[27]

The low number of events in each echogenicity group in our study calls for a cautious interpretation of the results. Although a significant linear trend was found, the confidence intervals were wide. A similar trend was observed for ipsilateral events, but the study did not have enough power to assess the independent effect of plaque morphology on ipsilateral events. Conclusions about whether plaque echolucency plays a causal role in the development of cerebrovascular ischemic events or merely acts as a marker of higher risk cannot be made on the basis of data from an observa-

tional study. The fact that the examiner knew whether a participant in the study had stenosis or not may have biased the results toward a greater difference between subjects with and without stenosis when it comes to clinical events, especially events like TIAs and amaurosis fugax, which are more susceptible to the subjective evaluation of the observer than stroke. We do not think, however, that this has led to substantial impact on the results. More importantly, the observer was blinded to plaque morphology, which makes it unlikely that any serious observation errors have biased the results in this respect. It is likely that the present study underestimates the true relationship between plaque morphology and risk of clinical disease because of random misclassification of plaque morphology.

TIA and amaurosis fugax are by definition transient, benign symptoms, which in themselves are no threat to the patient's health. They do, however, represent "warning signs" and as such are important predictors of stroke. Evaluation of plaque morphology in addition to the grade of stenosis might improve clinical decision-making and differentiate treatment for individual patients. Computer-quantified plaque morphology assessment, which is a more objective method of ultrasonic plaque characterization, may further improve this.[28] It has been suggested that plaque echolucency should be used to select patients with asymptomatic stenosis for carotid surgery,[6] but it is not known whether surgery is of greater benefit than medical treatment in subjects with echolucent stenotic plaques compared with subjects with echogenic plaques.

We conclude that plaque echolucency and degree of stenosis are independent predictors of stroke and cerebrovascular events. The present population-based study provides support for the concept that echolucent plaques are more likely to produce clinical cerebrovascular events.

Acknowledgments

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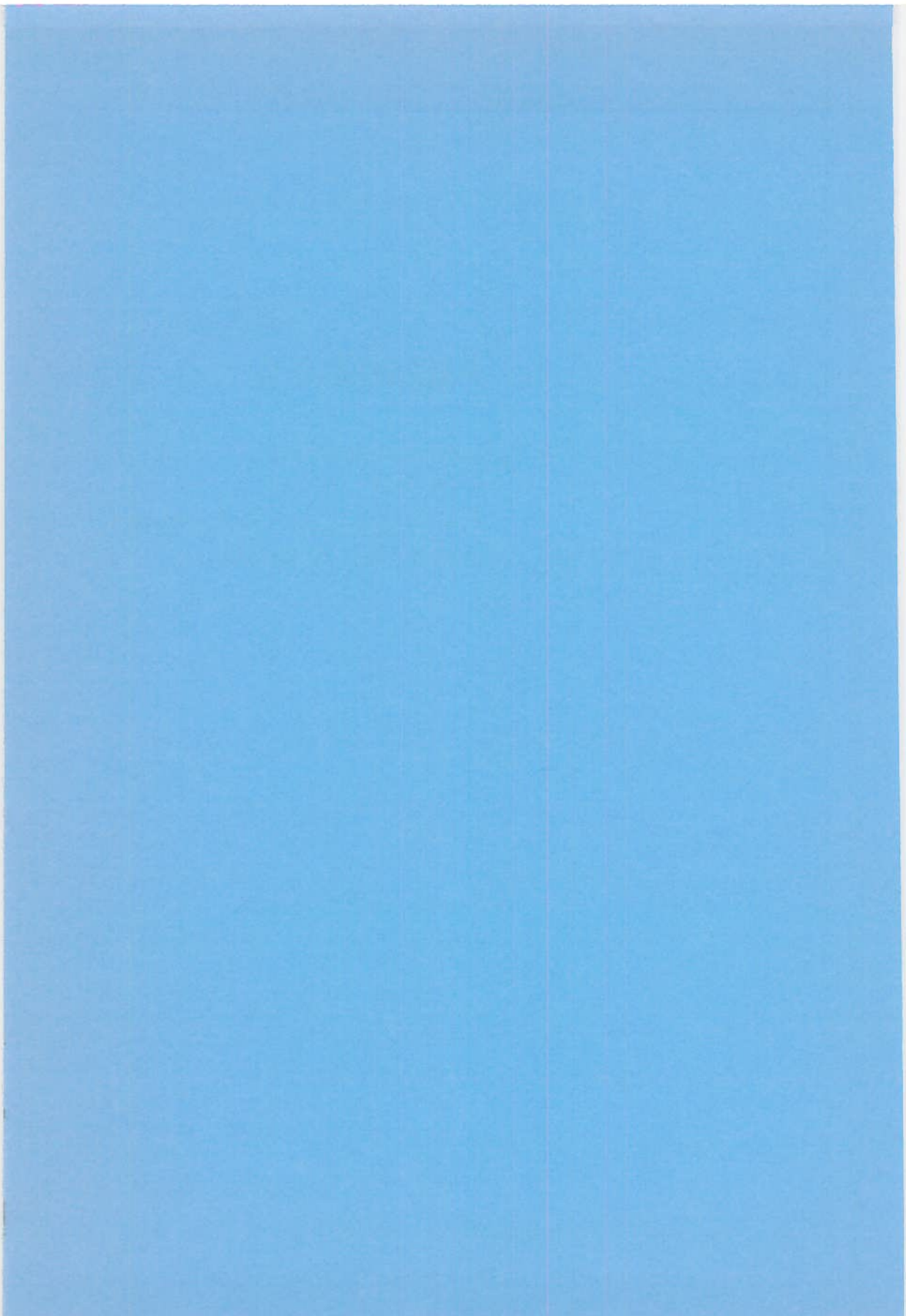
Appendix A

Information leaflet
First questionnaire,
Norwegian and English versions
Declarations of consent



Innbydelse til

HELSEUNDERSØKELSEN

TROMSØ

Fødselsdato Personnr. Kommune Kretsnr.

Velkommen til helseundersøkelsen i Tromsø!

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

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

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

Vennlig hilsen

Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

EGEN HELSE

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

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

Har du, eller har du hatt:

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

Bruker du medisin mot høyt blodtrykk?

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

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

Har du de siste to ukene følt deg:

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

MOSJON

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

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

KAFFE

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

		Antall kopper daglig
Kokekaffe	58	
Annen kaffe	60	

ALKOHOL

Er du total avholdsmann/-kvinne? 62 JA NEI

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

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65

Øl	Vin	Brennevin
glass	glass	glass

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

FETT

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

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

RØYKING

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

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

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

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? 41 Antall timer
Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv: JA NEI

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

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 45 Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig?	48	Antall sigaretter
Hvor gammel var du da du begynte å røyke daglig?	52	Alder
Hvor mange år tilsammen har du røykt daglig?	54	Antall år

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole	70	1
Realskole, middelskole, yrkesskole, 1-2-årig videregående skole		2
Artium, ok.gymnas. allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

Hva slags arbeidssituasjon har du nå?

Lønnet arbeid	71	
Heltids husarbeid	72	
Utdanning, militærtjeneste	73	
Arbeidsledig, permittert	74	

Hvor mange timer lønnet arbeid har du i uke? 75

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	76	
Attføring	81	
Uførepensjon	82	
Alderspensjon	83	
Sosialstønad	84	
Arbeidsløshetstrygd	85	

SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 65 JA NEI UVISS

English translation of invitation with the first questionnaire used in the health survey in Tromsø 1994/95

Translation based on translations by Kevin McCafferty and Anne Clancy

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. Come along even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure levels taken 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 ☐
- Not so good ☐
- Good ☐
- Very good ☐

Do you have, or have you ever had:

	YES	NO	Age first time
Myocardial infarction	☐	☐	_____ years
Angina pectoris	☐	☐	_____ years
Stroke/ brain haemorrhage	☐	☐	_____ years
Asthma	☐	☐	_____ years
Diabetes	☐	☐	_____ years

Do you take medicine for high blood pressure?

- At the moment ☐
- Used to, but not any longer ☐
- Never have ☐

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?

YES ☐ NO ☐

Have you in the last two weeks felt:

	No	A little	A lot	Very much
Nervous or worried?	☐	☐	☐	☐
Anxious?	☐	☐	☐	☐
Secure and calm?	☐	☐	☐	☐
Irritable?	☐	☐	☐	☐
Happy and optimistic?	☐	☐	☐	☐
Down/depressed?	☐	☐	☐	☐
Lonely?	☐	☐	☐	☐

Smoking

Did any of the adults at home smoke while you were growing up? YES ☐ NO ☐

Do you now, or have you previously, lived with daily smokers after your 20th birthday?

YES ☐ NO ☐

If "YES", for how many years in all? ____Years

How many hours a day do you normally spend in smoke-filled rooms? ____Hours

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

Do you yourself smoke:	YES	NO
Cigarettes daily?	☐	☐
Cigars/cigarillos daily?	☐	☐
Pipe daily ?	☐	☐

If you previously smoked daily, how long is it since you stopped? _____ Years

If you smoke daily at the moment, or have smoked before:

How many cigarettes do you smoke/did you smoke per day? _____ Cigarettes

How old were you when you began smoking daily? Age _____ Years

How many years in all have you smoked daily? _____ 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 pr. week None	Less than 1	1-2	3 or more
Light activity (*not sweating or out of breath*)	☐	☐	☐	☐
Hard activity (*sweating/ out of breath*)	☐	☐	☐	☐

Coffee

How many cups of coffee do you drink daily? *Put 0 if you do not drink coffee daily.* Cups

Boiled coffee ☐☐☐
(i.e., grind boiled and allowed to draw)
Other coffee ☐☐☐

Alcohol

Are you a teetotaler? 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.* ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? *Do not count low-alcohol beer. Put 0 if less than once a month.*

Beer Glasses	Wine Glasses	Spirits Glasses
☐☐	☐☐	☐☐

Fat

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

Don't use butter/margarine	☐
Creamery butter	☐
Hard margarine	☐
Soft margarine	☐
Butter/margarine blend	☐
Light margarine	☐

Education/work

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school, folk high school	☐
Technical school, middle school, vocational.. school, 1-2 years' senior high school	☐
A-levels/High school diploma, (3-4 years)	☐
College/university, less than 4 years	☐
College/university, 4 or more years	☐

What is your current work situation?

Paid work	☐
Full-time housework	☐
Education, military service	☐
Unemployed, redundant	☐

How many hours of paid work do you have pr. week? _____ Hours

Do you receive any of the following benefits?

Sickness benefit (sick leave)	☐
Rehabilitation benefit	☐
Disability pension	☐
Old-age pension	☐
Social welfare benefits	☐
Unemployment benefit	☐

Illness in the family

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

YES	NO	DON'T KNOW
☐	☐	☐

SAMTYKKEERKLÆRING

I invitasjonsbrosjyren til Helseundersøkelsen i Tromsø 1994-95, er jeg orientert om undersøkelsens formål. Jeg er kjent med at opplysningene blir behandlet strengt fortrolig og at undersøkelsen er godkjent av Datatilsynet og forelagt den forskningsetiske komité for Nord-Norge. Jeg er kjent med at jeg senere kan reservere meg mot bruk av opplysninger om meg.

Jeg samtykker i:

1. at melding om mine resultater sendes til min faste lege.
2. at blodprøven oppbevares til senere medisinsk forskning.
3. at mine resultater kan brukes til medisinsk forskning, eventuelt ved å sammenholde opplysningene om meg med opplysninger fra andre helse- og sykdomsregister (f.eks. kreftregister og dødsårsaksregister) og mine data fra de tidligere helseundersøkelsene i Tromsø.

Vennligst stryk det/de avsnitt du reserverer deg mot.

Tromsø, ...

Underskrift

SPESIALUNDERSØKELSEN '94-95

SAMTYKKE-ERKLÆRING

I invitasjonsbrosjyren til Spesialundersøkelsen i Tromsø 1994-95 er jeg orientert om undersøkelsens formål. Jeg vet at opplysningene blir behandlet strengt fortrolig og at undersøkelsen er godkjent av Datatilsynet og anbefalt av den regionale komite for medisinsk forskningsetikk. Jeg vet at jeg senere kan reservere meg mot bruk av opplysninger om meg.

Vennligst kryss av for det/de avsnitt du reserverer deg mot.

Jeg samtykker i:

☐ at melding om mine resultater sendes til min lege eller Regionsykehuset i Tromsø dersom jeg trenger videre undersøkelse eller behandling.

☐ at mine resultater kan brukes til medisinsk forskning, ved å sammenholde opplysningene med andre helse- og sykdomsregistre og opplysninger fra de tidligere helseundersøkelser i Tromsø.

☐ at blodprøven kan oppbevares og brukes til medisinsk forskning.

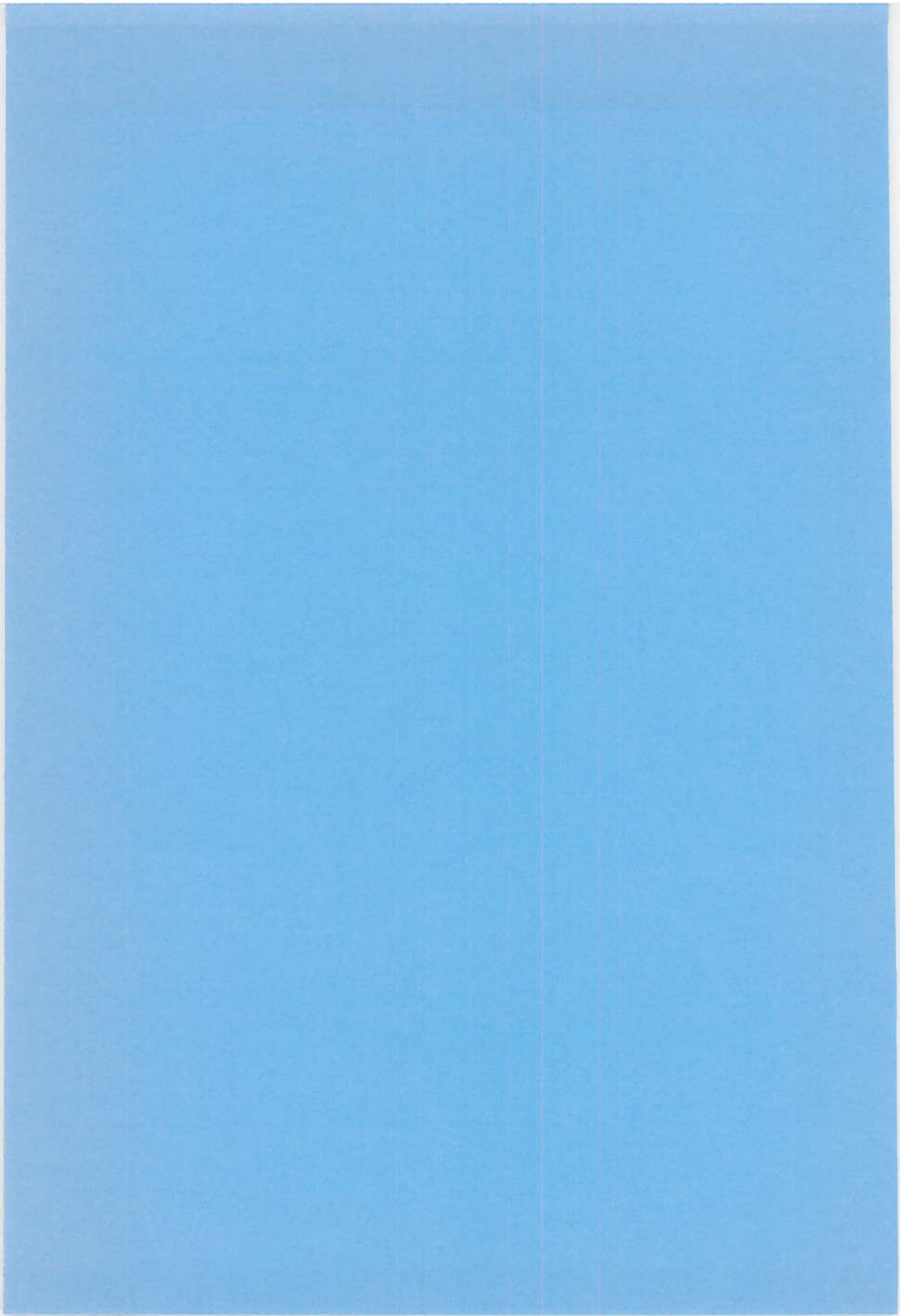
☐ at Helseundersøkelsen i Tromsø kan kontakte meg senere med forespørsel om å delta i undersøkelser.

Tromsø, ...

Dato Underskrift

Appendix B

Second questionnaires,
Norwegian and English versions



Helseundersøkelsen i Tromsø

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

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

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

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

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø **Statens helseundersøkelser**

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

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

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 ☐
- Gode ☐
- Vanskelige ☐
- Meget vanskelige ☐

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

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

BOLIG

Hvem bor du sammen med?

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

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

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

Hvor stor er din boenhet? ....46 _____ m²

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

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

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

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

ARBEID

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

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

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

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

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

EGNE SYKDOMMER

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

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

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

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

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

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

SYKDOM I FAMILIEN

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

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

SYMPTOMER

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

Hvor ofte er du plaget av søvnløshet?

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

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

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

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

Hvor ofte er du plaget av hodepine?

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

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

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

BRUK AV HELSEVESENET

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

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

LEGEMIDLER OG KOSTTILSKUDD

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

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

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

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

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

VENNER

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

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

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

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

KOSTVANER

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

Den rekker til omtrent 265 _____ skiver

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

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

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

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

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

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

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

ALKOHOL

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

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

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

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? ..... 312 _____ år

SLANKING

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

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

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

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

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

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

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

Dine kommentarer:

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 326 _____ år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... 328 _____ år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blødningsfri i minst 6 måneder? ..... 330 Ja ☐ Nei ☐

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

Hvis du fremdeles har menstruasjon eller er gravid:

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

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

SVANGERSKAP

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

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

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

Hvis "Ja", i hvilket svangerskap?

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

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

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

PREVENSJON OG ØSTROGEN

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

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

376 .....

Hvis du bruker eller har brukt p-pille:

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

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

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

Hvis du har sluttet å bruke P-piller:

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

Takk for hjelpen! Husk å postlegge skjemaet idag!

English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects younger than 70 years.

Based on translations by K. McCafferty and A. Clancy

TROMSØ HEALTH SURVEY

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions 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 nervous conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated 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 unsure 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. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year? _____

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

How was your family's economic situation while you were growing up?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

For how much of the first three years of your life

- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

For how much of the first 15 years of your life

- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

HOME

Who do you live with?

Tick once for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	_____
Other persons over 18 years	☐	☐	_____
Persons under 18 years	☐	☐	_____

How many of the children go to day care/kindergarten/ nursery school? ____

What type of home do you live in?

- Villa/ detached house ☐
- Farm ☐
- Flat /Apartment ☐
- Terraced /semi-detached house ☐
- Other ☐

How big is your home? _____ m2

Approximately what year was your home built? _____

	YES	NO
Has your home been insulated after 1970?	☐	☐
Do you live on the bottom floor/cellar level?	☐	☐
If "YES", is the floor laid on concrete?	☐	☐

What is the main source of heat in your home?

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

	YES	NO
Do you have fitted carpets in the living-room?	☐	☐
Is there a cat in your home?	☐	☐
Is there a dog in your home?	☐	☐

WORK

If you are in paid or unpaid work, which statement describes your work best?

- I am mainly seated while working (*e.g., at a desk/assembly work*) ☐
- My work requires a lot of walking (*e.g., shop assistant, light industrial work, teaching*) ☐
- My work entails a lot of walking and lifting (*e.g., postman/woman, nurse, building work*) ☐
- I do heavy physical work (*e.g., forestry, heavy agricultural/construction work*) ☐

Do you have any influence on how your work is organised?

- No, not at all ☐
- To a small extent ☐
- Yes, to a large extent ☐
- Yes, I decide myself ☐

	YES	NO
Are you on call; do you work shifts or nights?	☐	☐

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

Tick one box only for each item.	YES	NO
Driver	☐	☐
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	☐	☐	____
Wrist/forearm fracture	☐	☐	____
Whiplash	☐	☐	____
Injury requiring hospital admission	☐	☐	____
Stomach ulcer	☐	☐	____
Duodenal ulcer	☐	☐	____
An operation for stomach/ duodenal ulcer	☐	☐	____
Throat/ neck operation	☐	☐	____

Have you you ever had, or do you still have:

Tick one box only for each item.	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrome	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity:		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

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

_____ times

Have you had any of these in the last two weeks?

YES	NO
☐	☐

ILLNESS IN THE FAMILY

Tick the appropriate box for relatives that have, or have ever had the following illnesses: *Tick "None" if none of your relatives have had the condition.*

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Stomach/ duodenal ulcer	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Allergy	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough approximately every day of the year?	☐	☐
If "Yes": Is your cough productive ?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
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?	☐	☐

How often do you suffer from sleeplessness?

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

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

- No particular time of year ☐
- Especially during the dark winter months ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Have you in the last twelve months suffered from sleeplessness to the extent that it has affected your ability to work? YES ☐ NO ☐

How often do you suffer from headaches?

- Seldom/Never ☐
- Once a month or more ☐
- Once a week or more ☐
- Every day ☐

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

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

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	____
Psychologist or psychiatrist	____
Other medical specialist (not at a hospital)	____
Hospital out-patient clinic	____
Hospital admission	____
Medical officer at work	____
Physiotherapist	____
Chiropractor	____
Acupuncturist	____
Dentist	____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	____
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 every day or almost daily? Indicate how many months you used them for.
Write 0 for items you have not used.

Medication:

Painkillers	____ mths
Sleeping pills	____ mths
Tranquilizers	____ mths
Antidepressants	____ mths
Allergy drugs	____ mths
Asthma drugs	____ mths

Dietary supplements

Iron tablets	____ mths
Calcium tablets or bonemeal	____ mths
Vitamin D supplement	____ mths
Other vitamin supplements	____ mths
Cod liver oil or fish oil capsules	____ mths

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

Medicines	YES	NO
Painkillers	☐	☐
Antipyretic drugs (to reduce fever)	☐	☐
Migraine drugs	☐	☐
Eczema cream/ointment	☐	☐
Heart medicine (not blood pressure)	☐	☐
Lipid lowering drugs	☐	☐
Sleeping pills	☐	☐
Tranquilizers	☐	☐
Antidepressants	☐	☐
Other drugs for nervous conditions	☐	☐
Antacids	☐	☐
Gastric ulcer drugs	☐	☐
Insulin	☐	☐
Diabetes tablets	☐	☐
Thyroxin tablets (for metabolic disorder)	☐	☐
Cortisone tablets	☐	☐
Other medicine(s)	☐	☐

Dietary supplements	YES	NO
Iron tablets	☐	☐
Calcium tablets or bonemeal	☐	☐
Vitamin D supplement	☐	☐
Other vitamin supplements	☐	☐
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? _____ 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? _____

Do you feel you have enough good friends? YES ☐ NO ☐

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 ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

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. (i.e., 10-12g)

A catering portion is enough for about ____ slices.

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

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*
The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

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 cream milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Semi-skimmed milk (low-fat) (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Skimmed milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Tea (cups)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
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)	☐	☐	☐	☐	☐	☐
- brown cheese	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐
- jam and other sweet spreads	☐	☐	☐	☐	☐	☐

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	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner						
- meat	☐	☐	☐	☐	☐	☐
- sausage/meatloaf/ meatballs	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- fishballs/fishpudding/ fishcakes	☐	☐	☐	☐	☐	☐
- vegetables	☐	☐	☐	☐	☐	☐
Mayonnaise, remoulade	☐	☐	☐	☐	☐	☐
Carrots	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/ broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines	☐	☐	☐	☐	☐	☐
Sweetened soft drinks	☐	☐	☐	☐	☐	☐
Sugarfree ("Light") soft drinks	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐
Waffles, cakes, etc.	☐	☐	☐	☐	☐	☐

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	☐	☐	☐
1-2 times a month	☐	☐	☐
Roughly once a week	☐	☐	☐
2-3 times a week	☐	☐	☐
Roughly every day	☐	☐	☐

Approximately how often in the last year have you drunk alcohol that equals at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not in the last year ☐
- Just a few times ☐
- 1-2 times a month ☐
- 1-2 times a week ☐
- 3 or more times a week ☐

For approximately how many years has your alcohol comsumption been as you described above? _____ years

WEIGHT REDUCTION

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

- before age 20 _____ times
- after age 20 _____ times

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

- before age 20 _____ times _____ kg
- after age 20 _____ times _____ kg

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

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

Never ☐
Not more than once a month ☐
Two or more times a month ☐
Once a week or more ☐

Your comments:

Thank you for helping us! Remember to post the form today!
Tromsø Health Survey

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

If you no longer menstruate, how old were you when you stopped having menstruation? _____ years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more?

YES ☐ NO ☐

If "Yes", how many times? _____ times

If you still menstruate or are pregnant:
What date did your last menstruation begin?
day/month/year ___ / ___ / ___

Do you normally use painkillers to relieve period pains?
YES ☐ NO ☐

PREGNANCY

How many children have you given birth to? _____ children

Are you pregnant at the moment? YES ☐ NO ☐ Don't know ☐

During pregnancy, have you had high blood pressure and/or proteinuria? YES ☐ NO ☐

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

If you have given birth, fill out 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	_____	_____ months
2	_____	_____ months
3	_____	_____ months
4	_____	_____ months
5	_____	_____ months
6	_____	_____ months

CONTRACEPTION AND OESTROGEN

Do you, or have you ever, used:	Now	Used to	Never:
Contraceptive pills (incl.minipill)	☐	☐	☐
A hormonal intrauterine device	☐	☐	☐
Oestrogen (tablets or patches)	☐	☐	☐
Oestrogen (cream or suppositories)	☐	☐	☐

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

_____

If you use, or have ever used, contraceptive pills:

Age when you began taking the pill? _____years
How many years in total have you taken the pill? _____years
If you have given birth, how many years did you take the pill before your first child? _____years
If you have stopped taking the pill:
Age when you stopped? _____years

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 <u>siste</u> 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	☐	☐	☐
Oårlig 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	Flint brød	Knelp-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/ørr)	☐	☐	☐	☐
– 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

English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects 70 years or older.

Based on translations by Kevin McCafferty and Anne Clancy.

TROMSØ HEALTH SURVEY for the over 70s

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions 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 nervous conditions. The ultimate aim is to gain an overview of the general health of the elderly population. We would therefore like you to answer the questions below.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated 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 unsure 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. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year?

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

How was your family's financial situation while you were growing up?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

How old were your parents when they died?

- Mother _____ years
- Father _____ years

HOME

Who do you live with?
Tick one box for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	_____
Other persons over 18 years	☐	☐	_____
Persons under 18 years	☐	☐	_____

What type of home do you live in?

- Villa/detached house ☐
- Farm ☐
- Apartment/flat in block/terrace ☐
- Terraced/semi-detached house ☐
- Other ☐

How long have you lived in your present home? ____years

Is your home adapted to your needs? YES ☐ NO ☐

If "No", do you have problems with:

- Space ☐
- Variable temperature/too cold/too warm ☐
- Stairs ☐
- Toilet ☐
- Bath/shower ☐
- Maintenance ☐
- Other (please specify) ☐

Would you like to move into a retirement home?
YES ☐ NO ☐

PREVIOUS WORK AND FINANCIAL SITUATION

Which statement best describes the type of work you did for the last 5-10 years before you retired?

- I was mainly seated while working (*e.g., desk/assembly work*) ☐
- My work required a lot of walking (*e.g., shop assistant, housewife, teaching*) ☐
- My work required a lot of walking and lifting (*e.g., postman, nurse, construction work*) ☐
- I did heavy physical work (*e.g., forestry, heavy agricultural work, heavy construction work*) ☐

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

	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

How old were you when you retired? _____ years

What kind of pension do you have?

- Basic state pension ☐
- Additional pension ☐

How is your current financial situation?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse ☐
- No, unchanged ☐
- Yes, it has got better ☐

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

- Much worse ☐
- A little worse ☐
- About the same ☐
- A little better ☐
- Much better ☐

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	☐	☐	_____
Wrist /forearm fracture	☐	☐	_____
Whiplash	☐	☐	_____
Injury requiring hospital admission	☐	☐	_____
Stomach ulcer	☐	☐	_____
Duodenal ulcer	☐	☐	_____
Stomach/duodenal ulcer operation	☐	☐	_____
Throat/neck surgery	☐	☐	_____

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

	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrom	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Recurrent urinary incontinence	☐	☐
Glaucoma	☐	☐
Cataract	☐	☐
Arthrosis (osteoarthritis)	☐	☐
Rheumatoid arthritis	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flue), diarrhea/vomiting, or similar in the last six months?
_____ times

Have you had any of these in the last two weeks?
YES ☐ NO ☐

ILLNESS IN THE FAMILY

Tick off relatives who have, or have ever had, any of the following conditions:
Tick "None" for conditions which none of your relatives have had.

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Hypertension	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Arthrosis (osteoarthritis)	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough daily for periods of the year?	☐	☐
If "Yes":		
Is your cough productive?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
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?	☐	☐
Have you lost weight in the last year?	☐	☐
If "Yes": How many kilograms?	_____ kg	

How often do you suffer from sleeplessness?

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

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

- No particular time of year ☐
- Especially during the 'dark winter months' ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Do you usually take a nap during the day? YES ☐ NO ☐

Do you feel that you normally get enough sleep? YES ☐ NO ☐

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

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

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

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?

	Yes	With some help	No
Walking indoors on one level	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating meals	☐	☐	☐
Cooking	☐	☐	☐
Doing light housework (e.g., washing up)	☐	☐	☐
Doing heavier housework (e.g., cleaning floors)	☐	☐	☐
Going shopping	☐	☐	☐
Taking the bus	☐	☐	☐

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

Are you dependent on any of the following aids?

	Yes	No
Walking stick	☐	☐
Crutches	☐	☐
Walking frame/Zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device	☐	☐

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	_____
Psychologist or psychiatrist	_____
Other medical specialist (not at a hospital)	_____
Hospital out-patient clinic	_____
Hospital admission	_____
Physiotherapist	_____
Chiropractor	_____
Acupuncturist	_____
Dentist	_____
Chiropodist	_____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	_____
Healer, Faith healer, clairvoyant	_____

	Yes	No
Do you have domestic help?		
Private	☐	☐
Municipal	☐	☐
Do you receive services from the district nurse?	☐	☐

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

	Yes	No	Don't know
Assigned family GP	☐	☐	☐
District nurse	☐	☐	☐
Home assistance	☐	☐	☐

Do you feel confident that you can receive the health care and home assistance you require if you need it?

- Confident ☐
- Not confident ☐
- Very unsure ☐
- Don't know ☐

MEDICATION AND DIETARY SUPPLEMENTS

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

Medication:

Painkillers	_____ mths
Sleeping pills	_____ mths
Tranquillizers	_____ mths
Antidepressants	_____ mths
Allergy drugs	_____ mths
Asthma drugs	_____ mths
Heart medicine (not blood pressure)	_____ mths
Insulin	_____ mths
Diabetes tablets	_____ mths
Thyroxin tablets (for metabolic disorder)	_____ mths
Cortisone tablets	_____ mths
Remedies for constipation	_____ mths

Dietary supplements:

Iron tablets	_____ mths
Vitamin D supplement	_____ mths
Other vitamin supplements	_____ mths
Calcium tablets or bonemeal	_____ mths
Cod liver oil or fish oil capsules	_____ mths

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? Yes ☐ No ☐

If "Yes", who can give you help?

- Spouse/partner ☐
- Children ☐
- Others ☐

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

_____good friends

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

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

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

- Strong sense of belonging ☐
- Some sense of belonging ☐
- Not sure ☐
- Little or no sense of belonging ☐

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 ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

How many meals a day do you normally eat (dinner and smaller meals)? _____ Number

How many times a week do you eat a hot dinner? _____ Number

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

The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

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

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

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	6-
Milk of all types (glasses)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
Slices of bread with fish (e.g., mackerel in tomato sauce)	☐	☐	☐	☐	☐	☐
- cheese (e.g., Norwegia)	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐

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	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner - meat	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- vegetables (raw or cooked)	☐	☐	☐	☐	☐	☐
Carrots (raw or cooked)	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines, etc.	☐	☐	☐	☐	☐	☐

WELL BEING

How content do you generally feel with growing old?

- Good ☐
- Quite good ☐
- Up and down ☐
- Bad ☐

What is your view of the future?

- Bright ☐
- Not too bad ☐
- Quite worried ☐
- Dark ☐

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

How old were you when you stopped having menstruations? _____ years

PREGNANCY

How many children have you given birth to? _____children

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

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

During pregnancy, have you had high blood pressure and/or proteinuria? Yes ☐ No ☐

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

OESTROGEN

Do you, or have you ever used oestrogen:

	Now	Used to	Never
Tablets or patches	☐	☐	☐
Cream or suppositories	☐	☐	☐

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

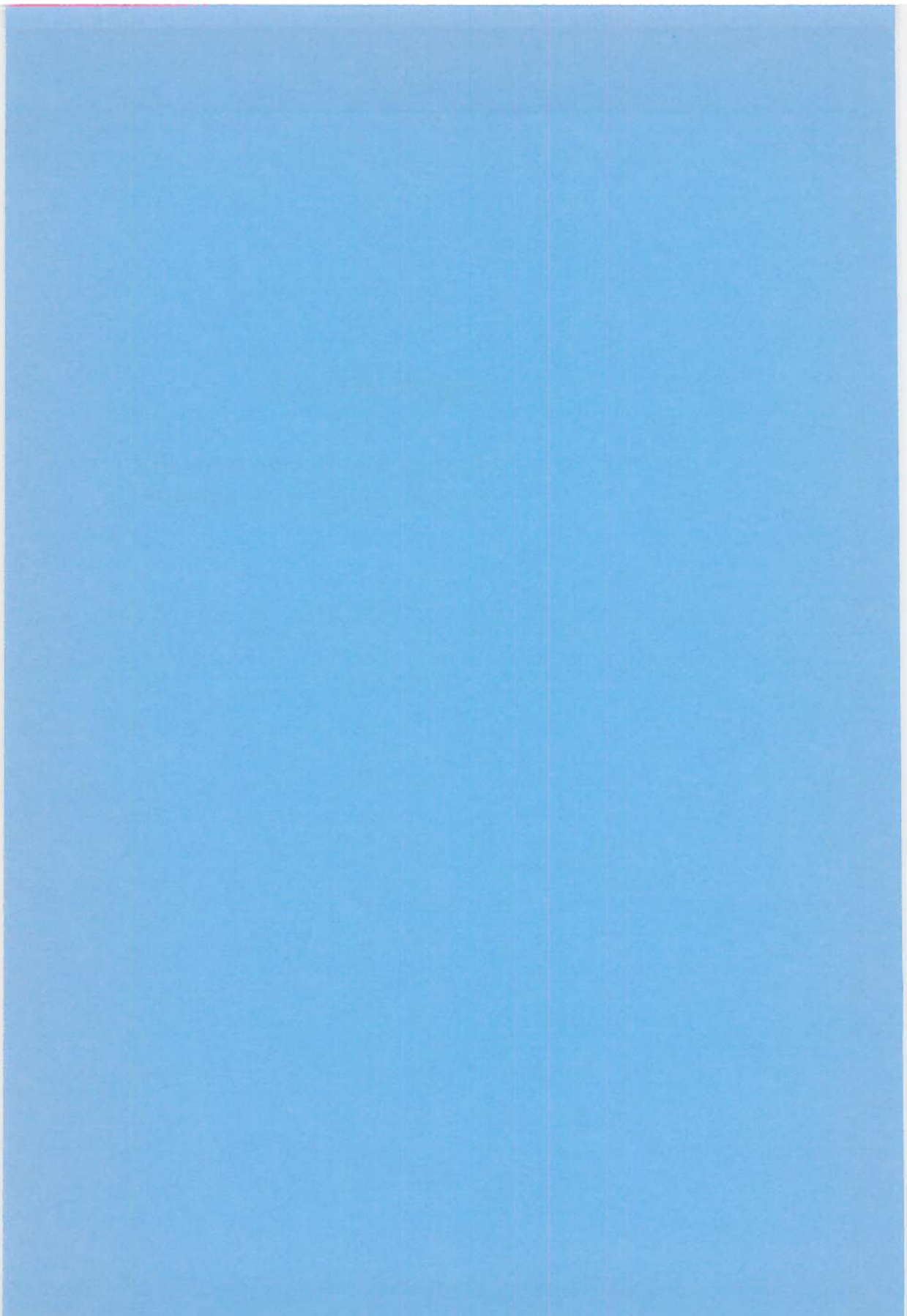
_____

Your comments:

Thank you for helping us! Remember to post the form today! **Tromsø Health Survey**

Appendix C

Measurements included in the fourth Tromsø Study 1994/95

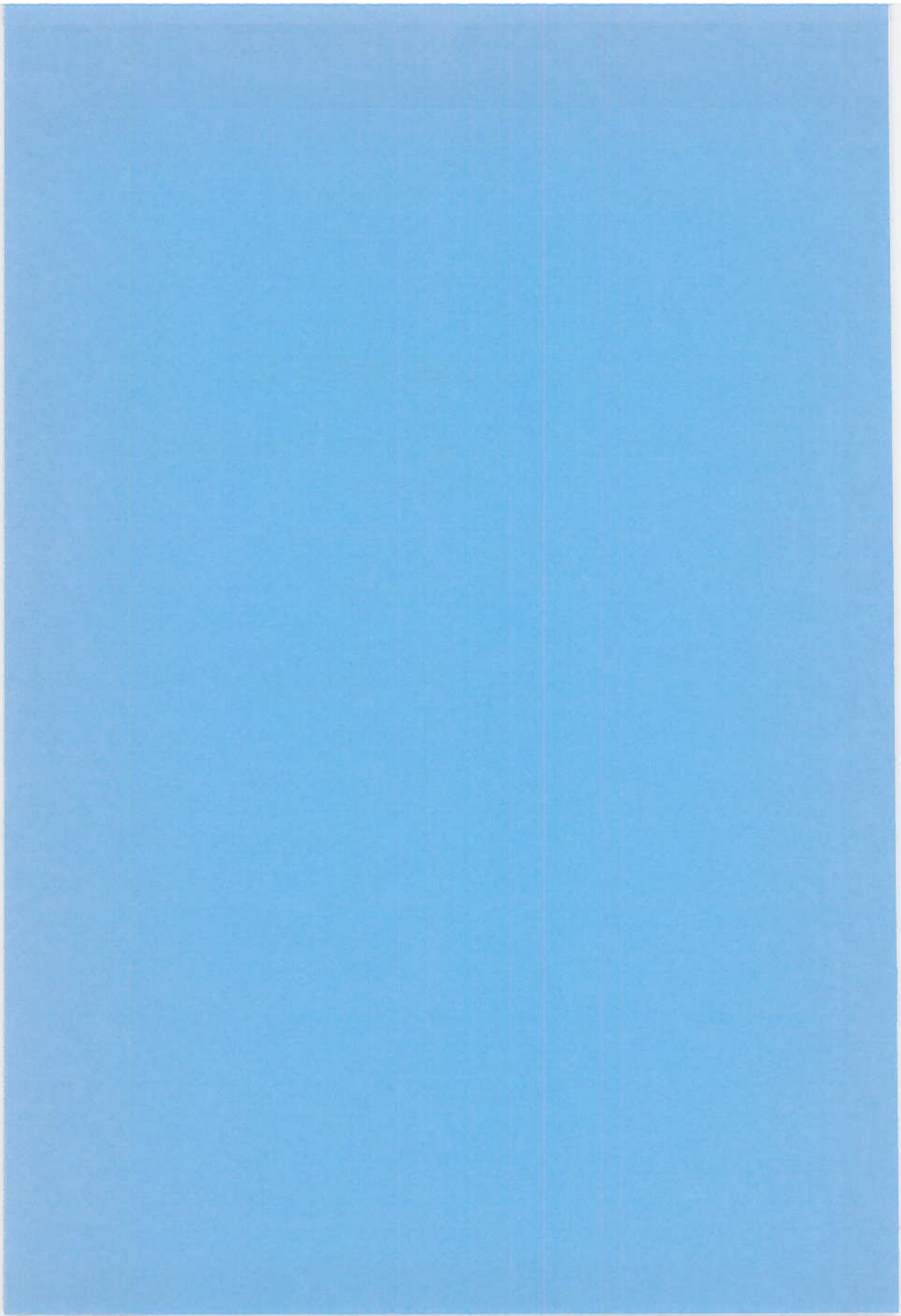


Measurements included in the fourth Tromsø Study 1994/95

	First Screening	Sec. Screening
Blood pressure	x	x
Heart rate	x	x
Height and body weight	x	
Waist/hip ratio		x
Urinary albumin /creatinine /stix /culture / NAG (3days)		x
Blood measurements:		
Total cholesterol	x	x
Triglycerids	x	x
HDL cholesterol	x	x
Non fasting serum glucose		x
γ-glutamyl transferase	x	x
Calcium	x	x
Ionised calcium and PTH	x	x
Creatinin		x
Non fasting insulin		x
Proinsulin		x
Glycosylated haemoglobin		x
Haemoglobin		x
Plot (blood cell count)	x	
Fibrinogen		x
Storage of serum	x	x
Storage of plasma	x	
Storage of blood cells	x	
Ultrasound carotis		x
Ultrasound aorta		x
Echocardiography		x
Bone density		x
Body fat composition		x
10-20 sec one-lead ECG	x	
10 sec 12 lead ECG		x
90 sec 8 lead ECG (R-R variability)		x
Questionnaires	x	x

Appendix D

Protocol for ultrasound screening procedures



PROCEDURES FOR MEASUREMENTS OF INTIMA-MEDIA THICKNESS AND RECORDING AND MEASUREMENTS OF PLAQUE OF THE RIGHT CAROTID ARTERY. THE TROMSØ STUDY 1994/1995

by
Oddmund Joakimsen

1. The Acuson ultrasound instrument is switched on.

2. A videocassette is inserted in the videorecorder.

3. Check that the videotape has been wound to the right position, do not overwrite previous recordings.

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 (Jon=1, Eva=2, Oddmund=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, number per artery, "missing measures" codings, etc).

6. A RES-field, appropriately adjusted to a maximum width of the screen and a depth of a little more than 2 cm of the B-mode image, is positioned on the screen for obtaining images from the carotid artery of optimal quality.

7. The subject is examined in a supine position with the head slightly rotated to the left. ECG-pads are attached to both arms and the right leg (or abdomen) (lead I), and the right carotid is insonated by a 5-7 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 (BIF), 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 as 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 wall of the artery. 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. A ultrasound examination sequence is then performed in the triplex modus (i.e., combination of pulsed wave Doppler, colour Doppler, and B-mode examination) from just above the clavicle and as high upstream above BIF as possible. The objective of this part of the examination is to look for stenotic areas along the artery. However, if plaques later during the B-mode scanning procedures are found suspicious of a hemodynamic significant stenosis, a new triplex examination is performed to reevaluate 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 in the near and the far wall.

    If a plaque is found, a frozen image of the vessel wall with the plaque presented as distinctly as possible and after 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 skewly 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.

The presentation of the plaque causing the largest thickness of the plaque is chosen for recording of a frozen image on the videotape. An electronic caliper is put on the top of the plaque (at the interface between the surface of the plaque and the vessel lumen) and another caliper in the presumed transition zone between the media and the adventitia layer. The distance between the calipers 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 BIF 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 cineloop containing more than 20 images. Afterwards, the images stored in the cineloop 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 BIF, the start of the BIF is first identified and then marked with an arrow. This is the point where the parallell walls of CCA are starting to diverge. If the probe throughout the recording process in the cineloop has changed position, the placeing 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 borderzone between BIF and CCA to avoid over- or underestimating of IMT.

The target site for IMT measurements of BIF is the 1 cm area from the start of the BIF 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 BIF still is recorded and marked MB, i.e., "missing bulb". If only one or two images from the cineloop is considered measurable, these are recorded and MB for one ore two images also recorded. IMT measurements from the near wall IMT in BIF were not recorded.

11. After examination of the BIF, B-mode scanning of CCA is performed, starting at the bifurcation 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, videorecording is performed of both the live sequence and of the frozen, marked images. Three optimal images for measuring IMT are chosen from the cineloop, from the arrow mark indicating the transition between BIF and CCA and 1 cm distally as described above. The images are marked CCA1, CCA2, and CCA3. Non-measurable images of IMT are also handled as described previously: an image of the CCA vessel wall is frozen and marked MC. All measurements on the far wall refer to the so-called "leading edge" principle (or "upper demarcation line" principle). These structures are not being different in thickness when the emitted power (mW/cm^2) or of the ultrasound instrument's gainsetting are changed (nor are biologic 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., gainsetting). Standardized examination conditions therefore are particularly important for 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.

After examination:

12. Do not remove the cassette from the videorecorder before end of the day, or when the cassette is full.

13. 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 BIF due to obesity
    MB 2= missing images from BIF due to a steep angle between CCA and BIF
    MB 3= missing images from BIF due to technically difficult examinations (e.g., short neck)
    MB 4= missing images from BIF 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.

14. 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 is used. Either a velocity increase across an atherosclerotic plaque in BIF of 0.1 m/sec or more or 0.2 m/sec or more 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 findings and clinical implications before leaving the room.

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1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
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6. Til professor Knut Westlund på hans 60-års dag, 1983.

7.* Blodtrykksovervåkning og blodtrykksmåling.
Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
Av Toralf Hasvold, 1984.

10. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
Av Georg Høyer, 1986.

11. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
Av Bjarne Koster Jacobsen, 1988.

12.* Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

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14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
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Av Roar Johnsen, 1992.

24. Diagnosis of pneumonia in adults in general practice.
Av Hasse Melbye, 1992.

25. Relationship between hemodynamics and blood lipids in population surveys, and effects of n-3 fatty acids.
Av Kaare Bønaa, 1992.

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27. Utdrag av medisinalberetninger fra Sulitjelma 1891-1990. **Av Anders Forsdahl, 1993.**

28. Helse, livsstil og levekår i Finnmark. Resultater fra Hjerte-karundersøkelsen i 1987-88. Finnmark III. **Av Knut Westlund og Anne Johanne Søgaard, 1993.**

29. Patterns and predictors of drug use. A pharmacoepidemiologic study, linking the analgesic drug prescriptions to a population health survey in Tromsø, Norway. **Av Anne Elise Eggen, 1994.**

30. ECG in health and disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972. **Av Per G. Lund-Larsen, 1994.**

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33. The Harstad injury prevention study: Hospital-based injury recording and community-based intervention. **Av Børge Ytterstad, 1995.**

34.* Vilkår for begrepsdannelse og praksis i psykiatri. En filosofisk undersøkelse. **Av Åge Wifstad, 1996.** (utgitt Tano Aschehoug forlag 1997)

35. Dialog og refleksjon. Festskrift til professor Tom Andersen på hans 60-års dag, 1996.

36. Factors affecting doctors´ decision making. **Av Ivar Sønbø Kristiansen, 1996.**

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38. Headache and neck or shoulder pain. An analysis of musculoskeletal problems in three comprehensive population studies in Northern Norway. **Av Toralf Hasvold, 1996.**

39. Senfølger av kjernefysiske prøvespreninger på øygruppen Novaya Semlya i perioden 1955 til 1962. Rapport etter programmet "Liv". Arkangelsk 1994.
Av A.V. Tkatchev, L.K. Dobrodeeva, A.I. Isaev, T.S. Podjakova, 1996.

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Av Helge Schirmer, Georg Høyer, Odd Nilssen, Tormod Brenn og Siri Steine, 1997.

41.* Physical activity and risk of cancer. A population based cohort study including prostate, testicular, colorectal, lung and breast cancer.
Av Inger Thune, 1997.

42. The Norwegian - Russian Health Study 1994/95. A cross-sectional study of pollution and health in the border area.
Av Tone Smith-Sivertsen, Valeri Tchachtchine, Eiliv Lund, Tor Norseth, Vladimir Bykov, 1997.

43. Use of alternative medicine by Norwegian cancer patients
Av Terje Risberg, 1998.

44. Incidence of and risk factors for myocardial infarction, stroke, and diabetes mellitus in a general population. The Finnmark Study 1974-1989.
Av Inger Njølstad, 1998.

45. General practitioner hospitals: Use and usefulness. A study from Finnmark County in North Norway.
Av Ivar Aaraas, 1998.

45B Sykestuer i Finnmark. En studie av bruk og nytteverdi.
Av Ivar Aaraas, 1998.

46. No går det på helsa laus. Helse, sykdom og risiko for sykdom i to nord-norske kystsamfunn.
Av Jorid Andersen, 1998.

47. The Tromsø Study: Risk factors for non-vertebral fractures in a middle-aged population.
Av Ragnar Martin Joakimsen, 1999.

48. The potential for reducing inappropriate hospital admissions: A study of health benefits and costs in a department of internal medicine.
Av Bjørn Odvar Eriksen, 1999.

49. Echocardiographic screening in a general population. Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease. The Tromsø Study.
Av Henrik Schirmer, 2000.

50. Environmental and occupational exposure, life-style factors and pregnancy outcome in artic and subartic populations of Norway and Russia.
Av Jon Øyvind Odland, 2000.

50B Окружающая и профессиональная экспозиция, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России
Юн Ойвин Удлан 2000

51. A population based study on coronary heart disease in families. The Finnmark Study 1974-1989.
Av Tormod Brenn, 2000.

52. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study.
Av Oddmund Joakimsen, 2000.

53. Risk factors for carotid intima-media thickness in a general population. The Tromsø Study 1979-1994.
Av Eva Stensland-Bugge, 2000.

54. The South Asian cataract management study.
Av Torkel Snellingen, 2000.

55. Air pollution and health in the Norwegian-Russian border area.
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57. Individual fatty acids and cardiovascular risk factors.
Av Sameline Grimsgaard, 2001.

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Av Anders Forsdahl, Fylkesnes K, Hermansen R, Lund E, Lupton B, Selmer R, Straume E, 2001.

59. Dietary data in the Norwegian women and cancer study. Validation and analyses of health related aspects.
Av Anette Hjartåker, 2001.

De som er merket med * har vi dessverre ikke flere eksemplar av.