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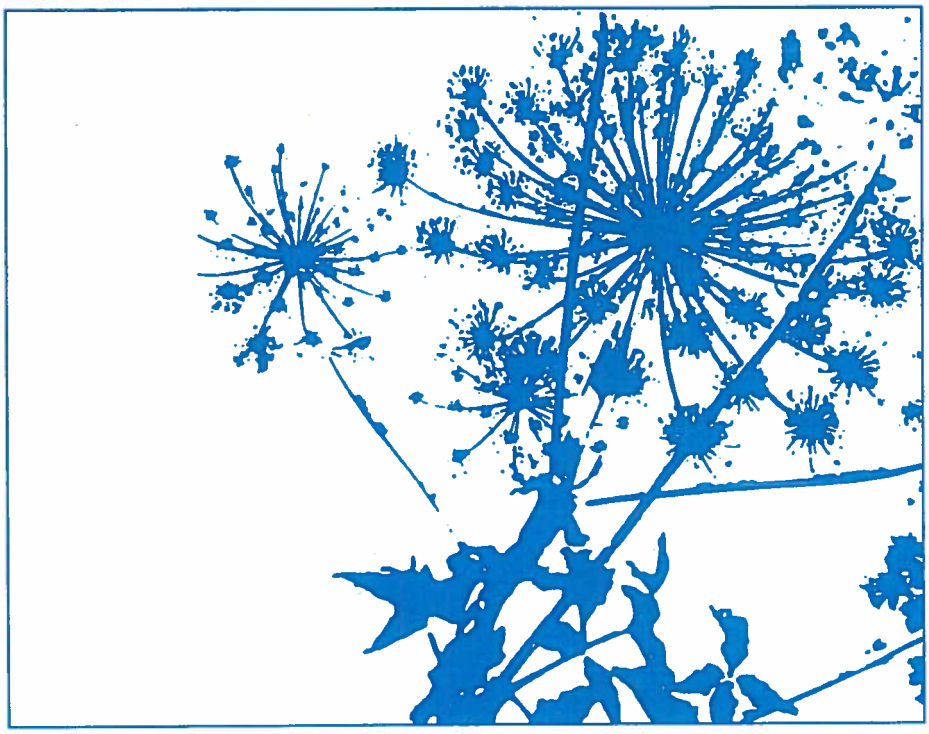

ULTRASOUND ASSESSED CAROTID ATHEROSCLEROSIS IN A GENERAL POPULATION

The Tromsø Study

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by
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University of Tromsø
Tromsø

Til Lisa

We dance in a ring and suppose. The secret sits in the middle and knows.

Robert Frost

CONTENTS

Acknowledgments

My warmest thanks go to some persons who probably never will read this thesis. These are all men and women who met to the fourth survey of the Tromsø Study 1994/95. Their attendance made this work possible. The annual follow-up examinations of mostly elderly persons with stenotic neck arteries have given me the opportunity to get acquainted with several people whose life experiences are typical for this generation of the coastal population of nothern Norway: Migration from small fishing and farming communities and into the more urban way of living in the town of Tromsø with all those social consequences of changes of lifestyle related to new occupations, educational demands, economical capacity, urban children and rural parents. It has been uttermost interesting lessons of the near history of my own homeland. Almost all of the persons had in common a genuine enthusiasm for the *scientific* purpose of all procedures they underwent.

Otherwise, substantial contributions to this thesis have come from many other sources. First, I want to express my gratitude to the Department of Neurology, Institute of Clinical Medicine and the Institute of Community Medicine, University of Tromsø – the former for letting me go for 4 years, the latter for letting me stay for as long a time. It has been somewhat of a surprise for me to experience this new world of scientific thinking and practising. A stay at an institute, at which research is the main activity, is highly recommended for us so-called experienced clinicians. The approach to scientific understanding and doing research is different from most clinical work. In my opinion, we clinicians too often inappropriately adopt or reject diagnostic or therapeutic methods due to occasional incidents, and do not consider that statistics sometimes "play a game of chance". On the other hand, doctors doing research for years should best keep some regular connection to clinical work so they can experience that the cases in their research are more than identity numbers linked to a lot of "observations". To avoid research on "buttonholes", doctors at scientific institutes are recommended to participate more regularly in clinical work or at least keep close contact with the clinical milieu in order to catch adequate research topics and making relevant scientific hypotheses. In my opinion, a continuous interchange of ideas and persons from both milieus is the optimal model for a mutual development of medical knowledge and competence.

I want to thank my colleagues at the Institute of Community Medicine for fruitful discussions and support throughout my time at the institute, and my colleagues at the Department of Neurology for reminding me all this time, by involving me in every-day clinical, neurological problems, that what I really am, is a neurologist.

I am very grateful for all support and help from the co-authors of the four articles: Kaare H. Bønaa, Eva Stensland-Bugge, Bjarne Koster Jacobsen, Ellisiv Mathiesen, and Egil Arnesen. Without their contributions, the articles probably never would have been accepted for publication. For those of us who already have utilized ultrasound data from the Tromsø Study 1994/1995, and for those who will continue to make use of these data in the future, we must be very indebted to "The third sonographer", my son Jon, who every day for one whole year made ultrasound examinations on more than half of all the 6727 subjects, sitting in the dark atmosphere of either the bathroom or the delivery room at the old "Kvinneklinikken". A great performance!

Lastly, I wish to express my sincere thanks to my supervisor Kaare H. Bønaa, who invited me to participate in the Tromsø Study. His help and support have been invaluable.

List of publications

The thesis is based on the following publications, that will be referred to by their Roman numerals (I-IV):

I: Joakimsen O, Bønaa KH, Stensland-Bugge E: Reproducibility of ultrasound assessment of carotid plaque occurrence, thickness, and morphology. The Tromsø Study. *Stroke* 1997;28:2201-2207

II: Joakimsen O, Bønaa KH, Stensland-Bugge E, Jacobsen BK: Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis. The Tromsø Study. *Arterioscler Thromb Vasc Biol* 1999; 19:3007-3013

III: Joakimsen O, Bønaa KH, Stensland-Bugge E, Jacobsen BK: Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis. The Tromsø Study. *J Clin Epidemiol* 2000; 53:525-530

IV: Joakimsen O, Bønaa KH, Mathiesen EB, Stensland-Bugge E, Arnesen E: Prediction of mortality by ultrasound screening of a general population for carotid stenosis. The Tromsø Study. Accepted for publication in *Stroke*

1. BACKGROUND

As a neurologist with a special interest in cerebrovascular diseases, and with several years of practice with ultrasound examinations of extra- and intracranial arteries, I have some times experienced patients in whom ultrasound revealed unexpected findings which surprised me, and made me wonder about etiological relationships and clinical implications. Thus, ultrasound examinations of the carotid arteries in some very old people showed smooth vessels without visible atherosclerosis, whereas in some young people with low cardiovascular risk factor levels, I found pronounced atherosclerosis with stenotic or occluded carotid arteries. Similarly, I have wondered why many patients with high-degree carotid stenosis did not suffer from ipsilateral ischemic cerebral stroke, whereas others who had a lower degree of stenosis experienced cerebral embolic events and had carotid endarterectomy. Was one of the causes that atherosclerosis might be a condition differing also in terms of pathogenicity?

Such unexpected and intriguing findings evoked my curiosity for a more scientific approach to carotid atherosclerosis. The opportunity arose when I was invited to participate in the fourth survey of the Tromsø Study.

1.1 Atherosclerosis

Atherosclerosis is a leading cause of mortality and morbidity, and it has become virtually epidemic in the Western world, affecting both sexes at all ages above infancy.[1; 2] Fortunately, in most individuals, atherosclerosis does not cause clinical disease. Of importance in reaching an understanding of its cause, is an appreciation of its variability among individuals and populations.[3] Until the last decade, population-based studies on the prevalence of atherosclerosis and the relationships between cardiovascular risk factors, atherosclerosis, and clinical diseases were not feasible due to lack of noninvasive diagnostic methods. However, autopsy studies have yielded substantial information of how atherosclerosis is distributed in populations.[3; 4] Autopsies are performed on a limited and

selected part of the subjects living in a community. Therefore, a major progress in the study of the natural history of atherosclerosis in populations occurred in the late eighties when noninvasive high-resolution B-mode ultrasound techniques were developed and used in population-based surveys.[5-7]

Ultrasound can detect minute atherosclerotic changes long time before the clinical manifestations of atherosclerosis appear. This has made it possible to study the early stages of cardiovascular diseases. By the time clinical manifestation occur, the artery is usually seriously diseased, and the lesions are characterized by atheronecrosis, fibrosis, mineralization, and/or ulcerations, clearly not the optimal time to begin interventions to regress or to arrest plaque progression or to improve vessel wall functions.

1.2 Ultrasonography

The basis for noninvasive and transcutaneous imaging of atherosclerosis is the technique of high-resolution ultrasound that has developed rapidly during the last two decades. Since its inception in the 1970s, grey scale (B-mode) ultrasound has achieved widespread use as a noninvasive, low-cost method for detecting disease in a variety of anatomic sites.

1.2.1 Basic principles

Ultrasound waves are processed from an oscillating piezoelectric crystal in the head of a handheld transducer, and transmitted as beams of waves with a certain frequency into human tissues. Some of the ultrasonic waves are reflected back to the transducer and received by the piezo element. The backscattered acoustic energy is converted to electrical signals which are sent to a computer where they are processed into a black-and-white image of the insonated anatomic structures. The depth of the structures is estimated by the computer from the time latencies between the emission and the reception of the same ultrasonic signals. Because the transducer transmits several parallell channels of ultrasonic beams (in our studies, the transducer had 128 electronically independent channels, simultaneously active in both transmission and reception) into the tissues, the backscattered ultrasonic beams reflect signals from different areas beneath the transducer, making it possible to obtain a spatial orientation of tissue components in the B-mode image. Part of the ultrasonic waves is absorbed, part is reflected to the transducer, and part is reflected astray (scattered) from anatomic structures in the field (Figure 1A and 1B). The strength of the reflection of ultrasound waves by the tissue

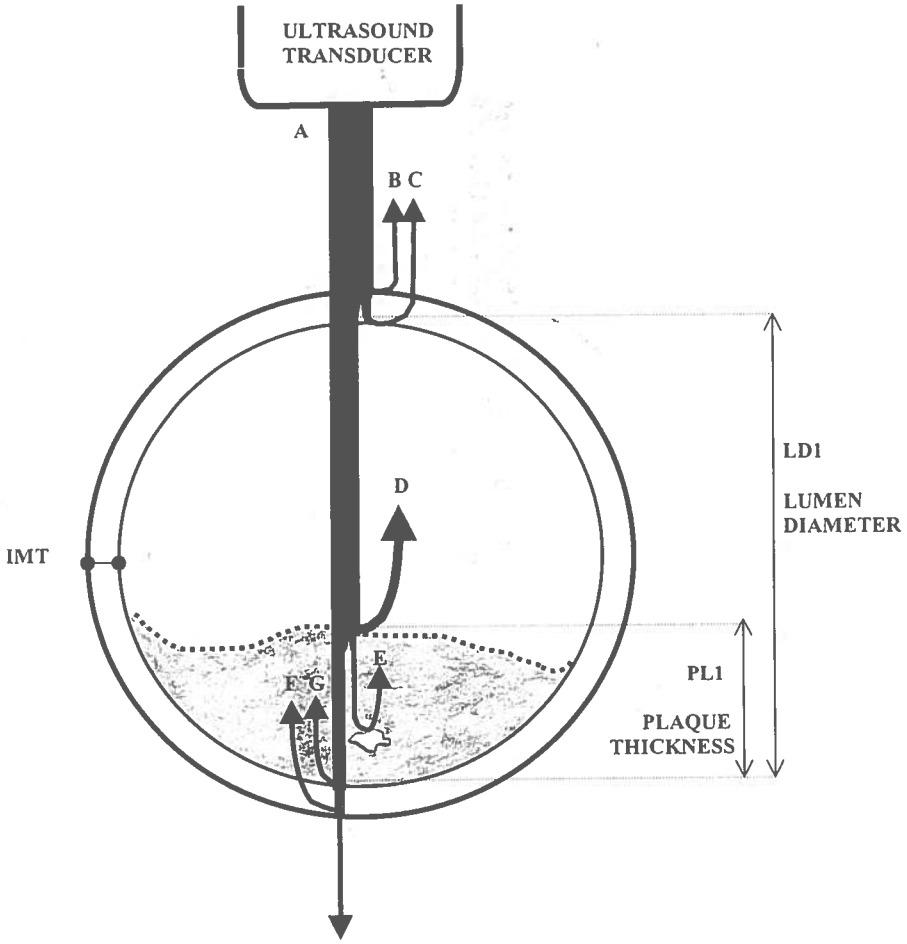

Figure 1A. A schematic illustration of an optimal propagation of ultrasound waves through an artery with an atherosclerotic plaque (crossectional view).

A denotes the ultrasound beam with the ultrasound energy reaching the near-wall of the artery. B and C denote ultrasound reflected to the transducer from the interfaces of periadventitia–adventitia and intima–vessel lumen. D denotes reflected echoes from the lumen-plaque interface, E, echoes from calcifications inside the plaque, and G and F, echoes from the lumen–intima and media–adventitia interface, respectively. (The interface G is normally not visible below an atherosclerotic plaque but has here been drawn as an illustration of its usual position.) PL1 denotes the true maximal plaque thickness, LD1, the true lumen diameter, and IMT, intima media thickness. The width of the arrows symbolizes the magnitude of ultrasound energy.

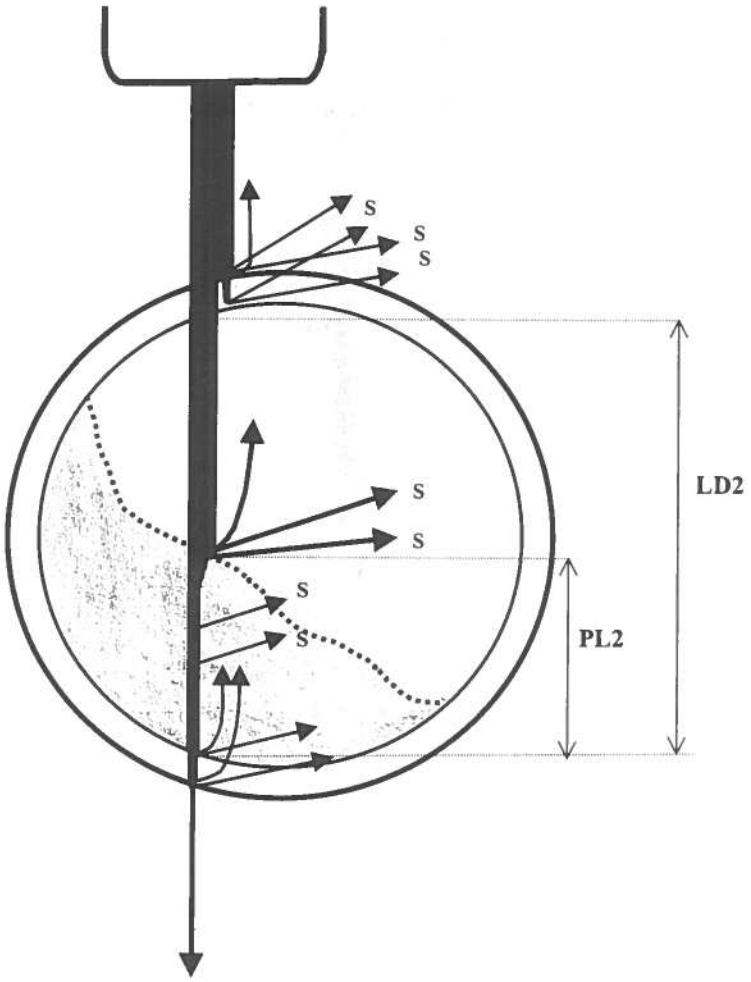

Figure 1B. A schematic illustration of nonoptimal propagation of ultrasound waves causing a distorted image of an artery with a plaque (crossectional view).

S means scattering of ultrasound away from the transducer causing reduced energy of reflected ultrasound. PL2 and LD2 illustrate falsely too large maximal plaque thickness and falsely too small lumen diameter.

(expressed as brightness of objects in B-mode images) depends on the differences of acoustic impedance between the different tissue layers. The higher the differences are, the more acoustic energy is reflected. If ultrasound had propagated through the tissues of the neck, and there had been no differences in acoustic impedance, nor would any reflection have occurred, and no structures would have been visible in the B-mode image. The acoustic impedance is dependent on the density of the tissue. Calcified tissues are strong ultrasound energy reflectors, appearing as white structures in the B-mode image, whereas fresh thrombi or blood are weak reflectors appearing black in images.

The magnitude of reflected energy also depends on the angle of the ultrasonic beams against the tissue object; when beams of ultrasonic waves are hitting an object (e.g., a vessel wall) perpendicularly, the reflection will be optimal (Figure 1A). Otherwise, some of the waves are scattered and reflected away from the transducer, and the quality of B-mode images may become insufficient for analytical purposes, with unsharp contours, loss of small structures, and distortion of proportions within the image (Figure 1B).

The ability to obtain informative ultrasound images depends not only on sufficient reflection of ultrasonic energy, but also on the resolution properties of the ultrasound instrument. The frequency of the ultrasound waves delivered from the transducer is the crucial factor for the ability to obtain detailed structural information from a B-mode image. With higher frequency, smaller objects and sharper edges of objects can be detected. However, the higher the emitted frequency is, the lower is the penetration of ultrasound waves through the tissues. The ideal frequency for insonating the carotid arteries is around 7 MHz.

The spatial resolution is the ability to discriminate small objects in the ultrasound field (detail resolution). The spatial resolution depends on many factors including the setting procedures of the ultrasound instrument (Appendix A). The spatial resolution consists of lateral and axial resolution components. The maximum lateral resolution depends on how many parallell, simultaneously active, and electrically independent ultrasound beam channels that are transmitting (and receiving) ultrasonic signals from (to) the ultrasound transducer.

The axial resolution is the ability to distinguish between two structures which are located in the same direction as the ultrasound waves, i.e., along the vertical axis compared to the skin surface. The maximum axial resolution of the equipment used in our studies is approximately 0.3 mm. The theoretical limitation of the axial resolution is set by the wavelength of the pulses of ultrasonic waves transmitted to the tissues. In addition to detail resolution, also contrast resolution and uniformity contribute to the quality of B-mode images.

Contrast resolution enables us to differentiate tissue types and to see subtle structures of different echodensities (e.g., whether the morphology of an atherosclerotic plaque is homo- or heterogenous). Uniformity refers to an image system's ability to provide comparable detail and contrast resolution throughout the field of view (primarily of different depths), which is important when characteristics such as size and appearance of plaques recorded from varying depths in different subjects are compared.

1.2.2 Doppler ultrasound

When moving objects, such as blood cells in arteries, are hit by ultrasound waves, they normally do not reflect ultrasound beams in a way that makes it possible to create B-mode images of "the body" of blood within the vessel. Blood consequently does not reflect ultrasound waves on B-mode ultrasound images, unless echographic contrast agents are injected. Blood in arteries therefore appears dark on black-and-white ultrasound images. If B-mode images show some white shading of the vessel lumen it normally means that the gain of the ultrasound instrument is set too high causing artifact signals from the lumen, or that the vessel is obstructed by obliterating atherosclerosis or a thrombus (Appendix A). The ultrasound instruments used in our studies had 256 shade gradients between black and white.

The ultrasonographic way to demonstrate circulating blood is by the Doppler effect. The frequency of the reflected sound beam waves may be shifted up or down as a result of its interaction with moving blood cells. The size of the Doppler shift is a measure of the blood velocity, and the increase of the frequency of the Doppler shift parallels the increase in velocity. Thus, across a stenosis where the lumen area is reduced to the half of the original, the Doppler shift (and blood velocity) increases to the double. This Doppler shift is recorded by the ultrasonic transducer, and the blood flow velocity is calculated by a computer. By sampling many Doppler signals from a larger part of an artery, the corresponding velocities can be calculated, and the resulting velocities values can be converted and mapped into a colour scale. This kind of colour Doppler imaging was introduced in the mid 1980s, and has refined the diagnosis of stenosis and other flow disturbances in arteries. This ultrasound modus is also helpful in delineating the outlines of atherosclerotic plaques (similar to conventional contrast arteriography). Sometimes the surface of a plaque consists of low-echogenic material, which makes it difficult to distinguish between dark, flowing blood and dark, low-echogenic objects on the plaque surface (e.g., a small thrombus). When adding

colour Doppler into the B-mode grey scale image, the outline of the protruding plaque is easier to detect, and more precise information of vessel wall abnormalities may be obtained.

1.2.3 Instrument adjustment

The various adjustment options, which can be utilized during ultrasound examinations, have been mentioned briefly in the Papers. Because the adjustments may influence the results, it is relevant to describe the meaning and implications of the adjustments more profoundly. This has been done in Appendix A.

1.3 Carotid atherosclerosis

The easy accessibility of ultrasound examinations of carotid arteries has made these arteries the main goal for *in vivo* studies of atherosclerosis[6, 8, 9]. The validity[10, 11] and reproducibility[12-14] of the ultrasound method are acceptable.[15] However, measures of carotid atherosclerosis are of limited value in epidemiologic cardiovascular research unless carotid atherosclerosis coincides with atherosclerosis in other arterial territories, e.g., in the coronary arteries. Both autopsy[4, 16, 17] and ultrasound studies[18-20] have found significant correlations between atherosclerosis in the carotid arteries and elsewhere in the arterial circulation.

Advanced stenotic carotid atherosclerosis is a predictor of cerebral stroke, and it has been shown that endarterectomy reduces the relative risk of stroke both in asymptomatic[21] and symptomatic subjects[22, 23]. The absolute risk reduction, however, is small, particularly among asymptomatic patients. Additional criteria have therefore been sought to select subgroups which may benefit more from surgery.

Not only the presence and size of carotid plaques but also the ultrasound assessed plaque morphology may predict cardiovascular disease.[24-27] In the International Atherosclerosis Project,[28] young subjects, who had fatty streaks in the coronary arteries with abundant extracellular lipid and monocytic cellular infiltration, were living in populations who had the highest risk of severe coronary atherosclerosis. It is now widely accepted that thrombotic coronary artery occlusion usually follows rupture or endothelial erosion of an unstable atherosclerotic plaque.[29] Postmortem studies of coronary and carotid arteries have shown that unstable plaques have a large core of extracellular lipid and/or necrotic cellular debris overlain by a thin, eccentric, fibrous cap, with evidence of inflammation.[30-32] Carotid plaques with these constituents appear echolucent ("soft") on ultrasound images.[33-35]. There are currently no practical means of detecting vulnerable plaques in the coronary arteries

noninvasively, and carotid plaque morphology classification has previously not been performed in population surveys.

2. AIMS OF THE THESIS

The main purposes of this thesis were to elucidate the following aspects of carotid atherosclerosis in a population health survey:

A) The reproducibility of ultrasound measurements of carotid plaque occurrence, size, and morphology.

B) The prevalence, distribution, size, and morphology of carotid plaques by age and sex.

C) The association between female reproductive factors and the prevalence and extent of carotid atherosclerosis.

D) The association between carotid stenosis and mortality.

3. SUBJECTS AND METHODS

The Tromsø Study is a population-based study on inhabitants of the municipality of Tromsø. The main objective is to obtain information about the distribution of predictors of cardiovascular disease, and to investigate associations between predictors and disease. Four population surveys have been conducted; in 1974, 1979/1980, 1986/1987, and 1994/1995.

The study population of this work comprised those men and women who participated in 1994/1995.

3.1 The Tromsø Study 1994/1995

The fourth survey of the Tromsø Study was carried out between September 1994 and October 1995. The survey was conducted by the University of Tromsø in cooperation with the National Health Screening Service and the local health authorities, and comprised two screening visits 4 to 12 weeks apart.

3.1.1 Subjects and questionnaires

All inhabitants older than 24 years were invited to the first visit, and all subjects aged 55-74 years and 5-10% samples in the other 5-year age groups older than 24 years were invited to both visits. The response rate by sex and age is shown in Table 1. A total of 6889 subjects, 79% of the eligible population, attended both visits. In the Papers I-III, figures of 6891 and 88% erroneously have been noted. The diverging number of attenders is due to a

computing error, and the error in the response rate arose because of errors in the data file of invited people.

Age (y)	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

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

In all, 6727 subjects, 3323 men and 3404 women, were examined by ultrasound of the right carotid artery. In addition, one of the sonographers (OJ) also examined the left carotid artery in 784 consecutive subjects at the end of the survey. This was done to obtain information on the prevalence of bilateral carotid stenosis. In Paper I, 7 subjects were inappropriately excluded due to a computing error. A total of 90% of those who met to visit I and were eligible for participation at visit II, attended visit II. In Paper I, this percentage erroneously was noted to be 98%. A flowchart of the selection of subjects to the various analyses in the thesis is shown in Figure 2.

In Paper II, 307 men, who belonged to a group of 323 men who had been specially invited to the fourth survey of the Tromsø Study, were excluded (Figure 2). A random 5% sample (n=16) of these 323 men were included, however. These 44-55 years old men (in 1994/1995) had been invited because they participated in a family intervention trial which was started after the second Tromsø Study in 1979.[36] The criteria for being allocated to this group were that they had values of total cholesterol in the highest decile and/or relative HDL cholesterol values (the ratio of HDL and total cholesterol) in the lowest quintile. Although

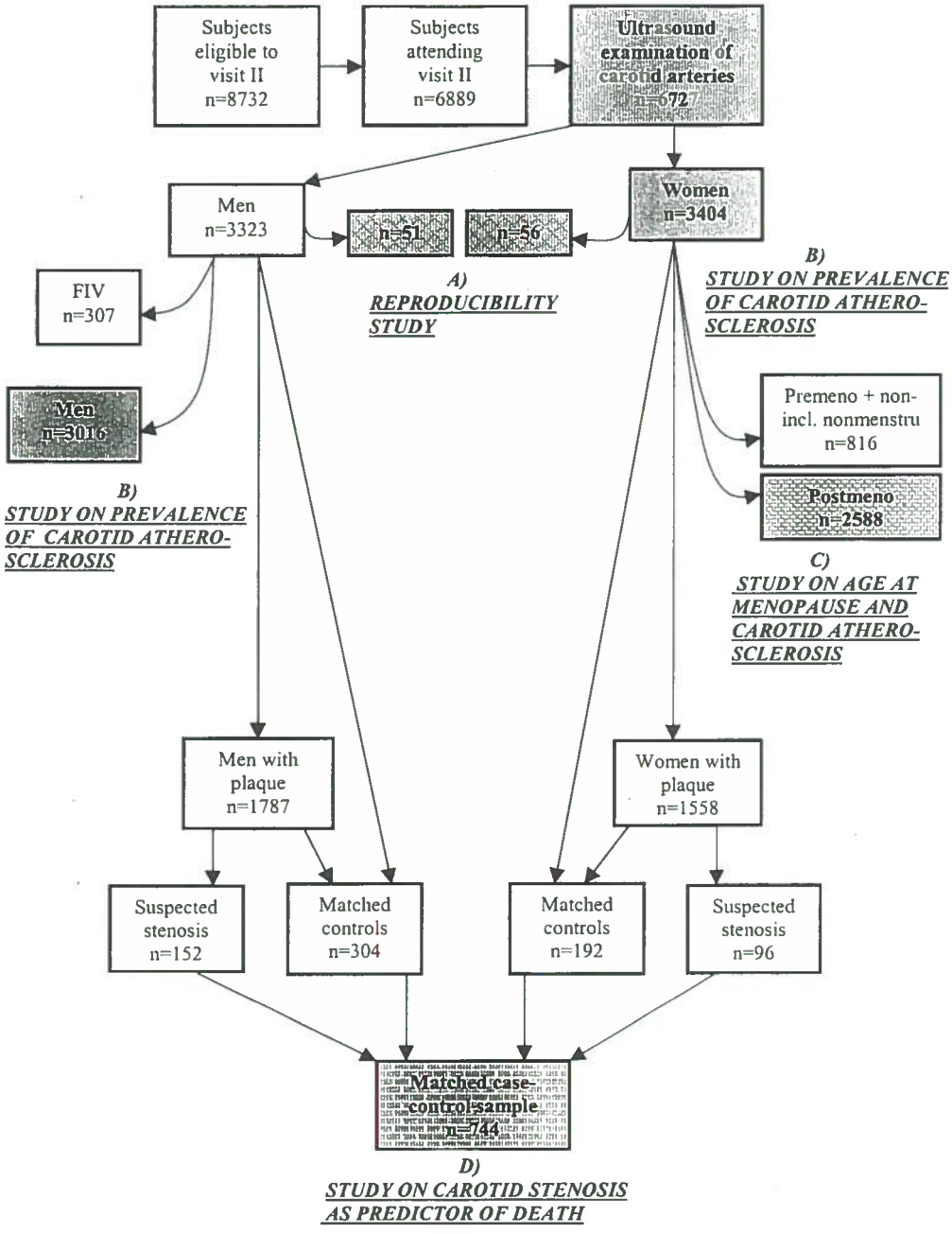

Fig 2. Flowchart of subjects examined by carotid ultrasound.

FIV denotes the Family Intervention Study. The characters A-D denote the four articles in the thesis.

half of this group was offered advice to reduce the risk factor levels, it was supposed that inclusion of these men would have given a biased estimate of the prevalence of atherosclerosis in these agegroups of men.

The subjects included in Paper III were postmenopausal women who reported cessation of menstruation ≥35 years and ≤60 years of age (Figure 2). The cause of cessation of menstruation was not specified in the questionnaire, and many of those who reported very early (<35 years) or very late menopause (>60 years) were suspected not to have had a natural menopause, and were therefore excluded to omit misclassification and biased results. To evaluate recall bias and the impact of other causes than a natural and spontaneous cause of menopause, all medical records of the 90 women who reported loss of menstruation in the age range of 35 to 39 years were scrutinized.

The questionnaires for both visits are presented in appendices B-D.

3.1.2 Ultrasonographic procedures

High-resolution B-mode ultrasonography was performed with an ultrasound scanner (Acuson Xp10 128 ART-upgraded, Mountain View, CA, USA) equipped with a linear array 5 MHz colour Doppler/pulsed wave Doppler and 7 MHz B-mode transducer. The ultrasonographic examinations were performed according to a protocol (Appendix E) written for the purpose of the current and forthcoming studies in Tromsø. To ensure equal and standardized examination techniques and measurement procedures, the three sonographers (one technician, one physician, and the author) completed a 2-month prestudy training protocol following the guidelines of the protocol in Appendix E. In addition, the first 200 ultrasound study examinations performed by the technician and the physician were supervised by the neurologist. The ultrasound examination procedures has been described in the four publications of the thesis and in Appendices A and E. The importance of standardized ultrasound examinations was underlined throughout the study. Classification of ultrasound morphology in terms of echogenicity and heterogeneity was performed according to guidelines in Appendix F. Similar ways of scoring ultrasound assessed plaque morphology has been reported previously.[26; 34; 37] As far as we know, our study was the first to utilize reference structures in the ultrasound image for optimizing the classification procedures, and also the first population-based study of intraplaque morphology.

3.2 The stenosis substudy

3.2.1 Subjects

Among the 6727 subjects examined with ultrasound, 248 subjects with suspected carotid stenosis and 496 age- and sex-matced controls (for each case, two matched controls were included) without suspected stenosis were included in the stenosis substudy (Figure 2). All subjects with suspected stenosis and one of the two controls were referred to further ultrasound investigations (including reclassification and grading of stenosis) and clinical examination at the outpatient clinic of the Department of Neurology, University Hospital of Tromsø. If one of the controls did not meet to the reevaluation, the second one was invited. A flowchart of the selection procedure is shown in Figure 1 of Paper IV.

3.2.2 Definition and quantification of stenosis

According to a specified protocol (Appendix G), carotid plaques were defined to cause stenosis if one or both of the two following criteria below were met: 1) Hemodynamic criterion: peak systolic velocity at the suspected stenosis (PSVs) ≥ 0.2 m/sec higher than peak systolic velocity at the point at reference (PSVr), or ≥ 0.1 m/sec if the stenosis was located in the bifurcation or the bulb of the internal carotid artery. The point of reference was the distal internal carotid artery as far upstream in the neck as technically possible to visualize. 2) Structural criterion: plaque causing 35% or more reduction of the lumen diameter on a longitudinal B-mode scan.

The hemodynamic criterion is routinely used in clinical work at the Department of Neurology both to define the presence of stenosis and as the method used in grading of stenosis. This comes from the era when pulsed wave Doppler examinations were the only method to calculate carotid stenosis noninvasively. In Paper IV, the degree of stenosis accordingly was calculated from velocity indices: 100% x (1 – PSVr/PSVs). Complete occlusion of the carotid artery was graded as 100% stenosis.

3.2.3 Follow-up

The ultrasound examination took place between September 1994 and October 1995 (when participants attended the survey), and those who were found to have suspected carotid stenosis and one of the two controls were reexamined at the Department of Neurology 1–4 months after they had been examined at the survey. The subjects were followed to either December 1st 1998 (the censoring date) or to the date of death before the censoring date.

Deceased subjects were identified by linkage to the Causes of Death Registry, and details of all deaths were documented whenever possible by hospital records and autopsy reports.

Cases were offered annual clinical and ultrasound follow-up at the Department of Neurology, while controls were not followed up after the clinical examination. The start of follow-up was different for the analyses based on data obtained at the screening (Analysis A in Figure 1, Paper IV) and the analyses obtained at the examinations at the outpatient clinic at the Department of Neurology (Analysis B in Figure 1, Paper IV).

3.3 Statistical analysis

All statistical analyses used in this thesis have been described in the papers I–IV.

4. MAIN RESULTS

4.1 Reproducibility (Paper I)

The three main findings were the following: It was possible, in the setting of a population-based study, to obtain: 1) substantial agreement on occurrence of carotid plaques both between and within sonographers with κ values (95% CI) of 0.72 (0.60-0.84) and 0.76 (0.63-0.89), respectively; 2) moderate reproducibility of plaque thickness measurements with mean absolute differences ranging between 0.25 and 0.55 mm, and coefficients of variation between 13.8% and 22.4%; and 3) high between- and within-sonographer agreement on plaque morphology classification, with κ values ranging between 0.54 and 0.73.

4.2 Prevalence of carotid atherosclerosis (Paper II)

Atherosclerotic plaques were found in 55.4% of the men and in 45.8% of the women. The prevalence of carotid atherosclerosis increased linearly with age in men, while in women, the increase in prevalence was curvilinear with an inflection at ≈ 50 years of age. The male predominance in atherosclerosis declined after the age of 50 years, the prevalence being similar in elderly men and women. Most of the plaqes were located to the bifurcation part of the common carotid artery both in men and women. Plaques in men were significantly softer (lower echogenicity) than plaques in women.

4.3 Age at menopause and carotid atherosclerosis (Paper III)

Women with late menopause had significantly less atherosclerosis than women with early menopause. The prevalence of plaque decreased with higher age at menopause (p=0.001

for age-adjusted linear trend). The trend remained significant (p=0.001) also after adjustment for confounding factors such as ever use of oestrogen, smoking before menopause, body mass index, length of education, and parity.

Postmenopausal women who had ever used oestrogen had significantly lower risk of carotid atherosclerosis than those who reported never use or did not answer the question about use of oestrogen replacement therapy.

4.4 Carotid stenosis as a predictor of death (Paper IV)

Among the 6727 men and women aged 25-84 years, who were screened with ultrasound, 248 subjects with suspected carotid stenosis were identified. These subjects and 496 age-and-sex matched controls were followed for 4.2 years. Mortality and cause of death were registered. The death rates were higher for those who had stenosis compared with those without stenosis. The death rates were approximately the same for those cases with stenosis who had clinical cardiovascular disease or diabetes, and those cases with stenosis who had no clinical disease.

The unadjusted relative risk (95% CI) for death was 2.72 (1.57-4.75) for subjects with stenosis compared with controls. Adjusting for cardiovascular risk factors increased the relative risk to 3.47 (1.47-8.19). The adjusted relative risk in persons with stenosis and no cardiovascular disease or diabetes was 5.66 (1.53-20.90), which was higher than in subjects with stenosis and selfreported disease; 1.79 (0.75-4.27). There was a dose-response relationship between the degree of stenosis and risk of death (p=0.002 for linear trend). Carotid stenosis was a stronger predictor of death than selfreported cardiovascular disease or diabetes.

5. DISCUSSION

5.1 Generalizability

It is a prerequisite for generalizability that the study results are valid. Internal validity of a study implies that findings do not depend on chance, bias, or confounding. External validity of an epidemiologic study means that the findings are applicable to other populations. Thus, generalizability is depending not only on the internal validity, but also on whether the study population is representative of other populations.

In the following, factors possibly influencing generalizibility of findings presented in the thesis are discussed.

5.1.1 External validity

There are no reasons to believe that participants in the fourth survey of Tromsø Study are notably dissimilar to inhabitants of other small cities and communities, at least in Scandinavia, with respect to demographic characteristics and cardiovascular risk factor levels. Differences in cardiovascular mortality between Scandinavian countries, countywise in Norway and between rural and urban areas are still present but to a lower extent than previously.[38-43] In Paper II, we show that the prevalence of atherosclerosis is similar in Tromsø compared to other populations, although study design varies slightly among different studies. It is therefore reasonable to believe that our conclusions may be of acceptable external validity.

5.1.2 Internal validity

Any observed association between an exposure and an outcome may not be true but can be due to alternative explanations. The association may simply be due to chance. Various types of biases can also detract from internal validity and distort the estimation of an epidemiologic measure. There are two main types of biases: selection bias and information bias. Counfounding is another possible alternative explanation for an observed observation. Chance and counfounding can be estimated quantitatively (if data of the confounding variable are available), whereas the effects of bias are more difficult or may even be impossible to take into account in the analysis. For this reason, it is of importance to design and conduct epidemiologic studies in such a way that risk of introducing bias is minimized.

In this thesis, evaluation of chance has been performed and described in the papers and mostly expressed by p-values and 95% confidence intervals. Confounding has also been dealt with in the articles. However, the role of some possible biases relevant for this thesis has not been discussed in the papers.

5.1.2.1 Selection bias

The wide age range (24 to 84 years) and high attendance rate (79%) of the participants of both visits in the fourth survey of the Tromsø Study make it likely that the results obtained are representative for the Tromsø population.

However, bias due to non-attendance in population surveys is well known.[44; 45] It is therefore not unlikely that such bias also may have occurred in the Tromsø Study IV. In other

studies, it has been found that non-responders had higher cardiovascular risk factor levels,[45] suffered more often from cardiovascular disease,[46; 47] and had higher death rates from most causes including coronary heart disease.[44; 47] In the second survey of the Tromsø Study,[48] however, only minor or no differences between responders and non-responders to questionnaires were found with regard to age, body mass index (BMI), blood lipids, and blood pressure, while responders more often were non-smokers.

We do not know the disease and risk factor status among non-attenders in the 1994/1995 survey. However, among men who attended the first, but not the second screening visit, there were more smokers and less married subjects. Male non-attenders above the age of 55 years had a higher level of education and lower total and HDL cholesterol values than attenders. Non-attenders younger than 55 years, reported more often a poor state of health. In other words, there was a rather inconsistent pattern with respect to risk factors for atherosclerosis among non-attenders [personal communication, Eva Stensland-Bugge, University of Tromsø].

If cardiovascular risk factor levels or disease status were higher among those who did not meet to the fourth survey of the Tromsø Study, a non-attendance selection bias may have occurred. The prevalence of carotid atherosclerosis (Paper II) and stenosis (Paper IV) may then have been underestimated. However, if more subjects with stenosis had attended the survey, the relative risk estimates for death among those with stenosis would not necessarily have been changed. The relative risk would have changed only if the relationship between stenosis and mortality differed between attenders and non-attenders.

Thus, if all invited subjects had met, the prevalences of carotid atherosclerosis probably would have been higher. For those participants with highest response rates and where whole age cohorts were invited (55 to 74 years), non-attendance is likely to have had a less impact on the results.

Non-attendance among elderly postmenopausal women may have influenced (weakened) the association between age at menopause and prevalence (and extent) of carotid atherosclerosis (Paper III). The mean age at examination of these women were 64 years, and it is likely that old women with an early menopause had developed more advanced atherosclerosis-related clinical disease than old women with late menopause, and thus, prohibiting those with early menopause from participating. Similarly, it is possible that more women in the category of low age at menopause already had died from clinical atherosclerosis before the ultrasound survey, causing a survival selection bias which also may have weakened

the relation between low age at menopause and atherosclerosis. However, the response rate was very high in these agegroups of women so non-attendance and survival selection biases probably are negligible.

Since the intention of Paper II was to present data on prevalence of carotid atherosclerosis in a general population, the specially invited 307 men with high total cholesterol and low HDL cholesterol were excluded from analyses to avoid selection bias (Paper II). It turned out, however, that this only had a minimal impact on the results.

In Paper IV, we chose to include all 6727 subjects because adjustments were done for total and HDL cholesterol in the Cox regression analyses. The only person among the 307 high-risk men who died during the follow-up period was one of the controls without stenosis. Thus, the consequence of excluding these high-risk men from the analyses would have been that the high relative risk of death among those with stenosis compared to those without would have been even higher.

The time for start of observation of cases with stenosis and control persons was set to two different dates for analysis A and B in Paper IV (Figure 1, Paper IV); the date for ultrasound screening for the former analysis, and the date for the clinical examination for the latter. This was done to avoid a potential selection bias which might have occurred if the one of the two selected controls, who were invited to the clinical examination and ultrasound reclassification, did not meet. If he/she could not meet, the other control person in the triplette was offered reexaminations. The reason for not meeting might have been serious disease or even death, and this could have caused a selection bias and a spuriously strengthening of the relative risk for death in the stenosis group.

5.1.2.2 Information bias

There are many potential sources of errors related to ultrasound measurements. Most errors are expected to be random, causing nondifferential misclassification that only can weaken the effects between any exposure and plaque occurrence, size, and morphology.

Information bias may have occurred if the participants told the sonographers during the ultrasound examination that they suffered from cardiovascular disease or had high risk factor levels. Although such knowledge was intended not to influence the examination, it is possible that more thorough examinations were done on these attenders "to try to find the plaque". Thus, an overestimation of prevalence and extent of carotid atherosclerosis in such subjects may have occurred. However, in order to obtain optimal images subjects had to be silent

during the ultrasound examination, and the time disposable for each subject was limited. We therefore do not think that possible knowledge about risk factors have influenced the results.

Obese people were more difficult to examine than other subjects due to their thick, short necks. Plaques might therefore have been overlooked, and optimal conditions for measurements of plaque thickness disturbed. This might have caused a measurement bias which could have weakened any association between BMI and carotid atherosclerosis.

Another possible information bias might have been erroneous selfreporting of cardiovascular disease. In Paper IV, the presence of carotid stenosis as a predictor of death was analysed in subjects with and without selfreported diseases or diabetes, and in some of the Cox regression analyses, selfreported cardiovascular disease was treated as a possible confounding variable. The history taken from and clinical examinations (which also permitted admission to the medical records) performed on subjects with and without stenosis who participated in the follow-up examination (Analysis B in Figure 1, Paper IV) made it possible to validate the participants' selfreported history of stroke, myocardial infarction, and angina pectoris. Table 2 shows that the specificity for all three conditions were high, whereas the sensitivity was lower, particularly for stroke. However, when validated in stead of selfreported cardiovascular disease was used in the analyses in Paper IV, it was found that the misclassification had only minor influence on the results.

Recall bias due to long time from menopause to participation in the Tromsø Study IV may have occurred. The longest time since menopause (mean time ≥20 years) was experienced by 90 women who reported a very low age at menopause (35-39 years). When the medical records of these 90 women were examined, we found that 7 of them actually were between 40 and 53 years old when they had their menopause. (One of these was a 40 years old woman who reported that she had experienced menopause. However, according to the medical records, she some months later gave birth to a child!)

This is an example of a non-random, differential misclassification of menopause age categories. This kind of misclassification, where errors in exposure (here: age at menopause) are associated with endpoint status (here: presence of carotid plaque) might cause both an exaggeration or an underestimating of an effect.[49] Because plaques more often were found in the group of women with low age at menopause, the bias in this case most likely weakened the association between age at menopause and atherosclerosis.

Table 2. Sensitivity, specificity, and predictive values positive for 464 subjects with and without carotid stenosis who reported cardiovascular disease.

	Validated stroke		
Selfreported stroke	Yes	No	Total
Yes	17	7	24
No	14	423	437
Total	31	430	*461**
Sensitivity = 55 %	*Specificity = 98 %*		*Predictive value positive= 71 %*

	Validated angina pectoris		
Selfreported angina pectoris	Yes	No	Total
Yes	82	10	92
Negative	33	335	368
Total	115	345	*460**
Sensitivity = 71 %	*Specificity = 97 %*		*Predictive value positive = 89 %*

	Validated myocardial infarction		
Selfreported myocardial infarction	Yes	No	Total
Yes	50	5	55
No	11	395	406
Total	61	400	*461**
Sensitivity = 82 %	*Specificity = 99 %*		*Predictive value positive = 91 %*

*The reason for missing values is that some subjects did not report this disorder in the questionnaire.

In the questionnaires (C,D), the female participants were asked about age when they had their last menstruation but they were not asked about any hysterectomy or oophorectomy. No information about the nature of menopause was therefore *a priori* available. Because natural and surgical menopause have been found to have differential impact on cardiovascular disease and death,[50] it was possible that this unresolved issue might have influenced the

results presented in Paper III. The effect on atherosclerosis of these two different causes of surgical menopause may be expected to be opposite relative to a natural menopause; hysterectomy leaves, at least for the first postoperative years, an approximately normal ovarian function, while oophorectomy (bilateral) causes a more abrupt and substantial reduction of oestrogen synthesis than a natural menopause. Since menopause due to surgery was most likely to have occurred among those who reported a very low age at menopause (35-39 years), we examined the medical records of those 90 women. The analyses were done both with all women included, and also after exclusion of those who had a surgical menopause. No notable differences were found (Paper III).

Another problem concerns the use of hormone replacement therapy (HRT). Women were not asked about whether or not menstruation stopped before they started HRT, and some women therefore might have reported a later menopause than the natural due to prolonged bleedings caused by HRT. Misclassification due to such a misreporting is probably of minor significance since both use of HRT and late natural menopause are protecting factors against atherosclerosis. Questions about use of oestrogen were not answered by 610 out of 2588 postmenopausal women, which may suggest that these questions were not sufficiently precisely addressed.

5.1.2.3 Confounding

Confounding can be defined as the effect of a third variable on both an exposure and an outcome variable that distort the true association between exposure and outcome. Confounding can lead to an underestimate or an overestimate of the association and even change the direction of the observed effect. In Paper III, the confounding variables, particularly the smoking variable, deserve special comments. The study reported in Paper III is a retrospective cohort study, and both the exposure (low age at menopause) and the outcome (carotid atherosclerosis) have occurred at the start of the investigation. In this study, a confounding variable is a variable which is associated with both age at menopause and atherosclerosis. If a person has started to smoke after cessation of menstruation, smoking has no causative influence on age at menopause. However, since previous smoking is related to current smoking, smoking habits at the screening still may be a confounding factor because confounding must only be associated with and not necessarily causatively related to both the predictor and the outcome.

In the analyses of Paper III, smoking (yes/no) before menopause was used because smoking habits before menopause were known. The number of years of smoking before menopause also was known, and smoking as a continuous variable was tested to evaluate any dose-response relationship of this smoking variable. However, because only a few of these mostly elderly women had smoked before menopause, this statistical analysis did not add information compared with the use of the dichotomous premenopausal smoking variable.

Obesity before menopause may also be an important confounder because of its likely impact on both age at menopause and atherosclerosis. Since the values of BMI at the time of menopause were not known, BMI measured at the survey had to be used in the analyses. Although high correlation between these BMI values and values measured before menopause has been found,[51] the interpretation of the effect of obesity on the relation between age at menopause and carotid atherosclerosis must be cautious.

5.2 Results

5.2.1 Reproducibility.

How should reproducibility of ultrasound measurements be estimated, and how should the results be presented to readers in order to provide relevant information on precision of such measurements? With respect to reproducibility on plaque thickness, we presented coefficients of variation (CV) of differences between measurements (Paper I), similarly to what had been reported in other studies.[52, 53] Such CV estimates are, however, not intuitively easy to comprehend. The formula for the CV for differences is not identical with the usual formula for CV (i.e., the standard deviation of all thicknesses measurements expressed as a percentage of the mean of thicknesses).

Reproducibility on plaque thickness measurements was also presented as mean absolute differences of plaque thickness between and within sonographers (Paper I). However, the values of mean absolute differences alone are also of limited value for the understanding of reproducibility. Some sort of a "plaque thickness index" with the mean absolute difference between paired thickness measurements as a numerator and the mean plaque thickness in the study group as denominator might have given a better illustration of variability. It has been suggested that such a "plaque thickness index" should be used.[13] The best illustration of the reproducibility of plaque thicknesses, however, may be to plot the differences against means of paired thicknesses of plaques ("Altman's plot"), as shown in Paper I.

Agreement of plaque morphology scoring has not been done before on data from population-based studies. We found acceptable reproducibility. However, our results were derived from off-line registrations of plaques. After publication of Paper I, further studies on reproducibility of plaque morphology have been reported. One of these was on plaques from those in our own population who had carotid stenosis.[54] The agreement of plaque echogenicity was calculated from on-line images of carotid arteries (i.e., during the ultrasound imaging process) and not from off-line, video-recorded images, which was done in Paper I . The agreement was not notably different from what was reported in Paper I despite the additional source of between- and within-observer variation that is related to on-line compared to off-line evaluation. In contrast, an other study concluded that interrater reliability of plaque morphology classification was low with κ-values below 0.3.[55] This study was on patients with high-degree carotid stenosis (80–99%), and the categorization of echogenicity was somewhat different from ours.

5.2.2 Prevalence of carotid atherosclerosis.

Although the prevalence figures of atherosclerosis for the oldest and youngest men and women indicated a sex difference, it should be noted that these prevalence figures are based upon only 5% samples of the population in these agegroups (Figure 2, Paper II). The uncertainties about prevalence estimates are furthermore underlined by the lower reponse rates in these agegroups (Table 1).

We decided to exclude the specially invited 307 high-risk men with high total cholesterol and low HDL cholesterol values. However, if these men had been included, the results had not changed notably (data not shown). This finding may be an illustration of the robustness of large population-based studies.

5.2.3 Plaque morphology

Women were found to have harder plaque than men (Paper II), and we hypothesized that the higher male/female ratio found in studies on clinical coronary disease compared with the male/female ratio for carotid atherosclerosis, may be due to a more benign atherosclerosis in women. A recent study[56] found that women admitted to the hospital with acute coronary syndromes were significantly less likely to have a clinical presentation associated with occlusive thrombus. They postulate that some anatomical difference in atherosclerosis of men and women may be one of the underlying reasons for the sex difference. The authors also

referred to studies showing that men "get infarctions, women have angina". In our population of ultrasound assessed subjects, 10.9% of the men and 7.8% of the women reported angina pectoris, while almost three times more men (9.2%) than women (3.2%) reported that they had suffered a myocardial infarction.

Previous studies showed that women more often than men got serious complications after percutaneous transluminal angioplasty[57] and aortocoronary bypass[58] also after adjustment for body surface area,[59] which is a proxy for the size of coronary arteries. This may be due to a "harder and more friable" coronary atherosclerosis in women consistent with our findings.

Another recent study[60] did not, however, find any sex difference in coronary artery morphology when performing intravascular ultrasound. But their measures of plaque morphology were restricted only to whether calcium deposits were present or absent in plaques, why it is difficult to compare their findings with ours. In addition, patients included in this study were those who had stable angina pectoris, and thus, a selected group of men and women with stable, hard plaques may have been studied.

We postulated in Paper I (p. 2206) and Paper II (p. 3012) that if coronary and carotid artery plaques shared common morphological characteristics, then soft carotid plaques may herald serious coronary heart disease. A recent study suggests such a relationship,[61] although this study was based on plaque surface characteristics ("irregularities") assessed by carotid angiograms. Their conclusion that some individuals have a systemic predisposition to irregularity and rupture of atherosclerotic plaques is important in the context of this thesis. The rupture of small, soft plaques is a main pathogenetic mechanism of acute coronary syndromes.[62-66] It is possible that persons with echolucent plaques should receive aggressive, prophylactic treatment.

In contrast to coronary heart disease, it has been been more uncertain whether carotid plaque morphology is an independent risk factor for stroke. Soft carotid stenotic plaques have been shown, however, to be associated with stroke.[25-27] Recent studies have shown that plaque instability usually is the cause of fatal thrombotic carotid occlusion,[31] and MRI-verified structural changes (infarctions, white matter hyperintensities, or atrophy) also have been found to be associated with plaque morphology, both surface irregularities and ultrasound density.[67]

5.3 Ethical aspects

Previous surveys in Tromsø measured traditional cardiovascular risk factors such as blood pressure and lipids (cholesterol and triglycerides). Information about abnormal findings

have been communicated to the subjects either by the physicians engaged in the study or by reports to the general practictioners who informed and performed follow-up examinations of the participants.

In the fourth survey of the Tromsø Study, more clinically related examinations such as echocardiography, ultrasound of the abdominal aorta, bone densitometry, and ultrasonographic evaluation of the carotid artery were performed. What should be done when abnormalities were found? Regarding carotid ultrasound, the problem was how to define those abnormal findings that necessitated information to the study participants and referral to further ultrasound and clinical examinations.

We decided to tell those who asked whether there was "anything wrong?" and who had plaque, but not stenosis according to our definition, that this finding was of no clinical significance, and that follow-up was unwarranted. This approach was considered appropriate as far as no reports had shown any benefit from diagnostic or therapeutic intervention on those who have plaque. In contrast, the participants who were suspected to have carotid stenosis according to preset criteria were offered clinical examination and ultrasound reinvestigation at the outpatient clinic. They were reassured about their low risk of stroke, and clinical examination and ultrasound reevaluation were offered and in far most cases, arranged shortly after the survey.

It is an inherent problem of this kind of surveys that abnormalities may be disclosed and some subjects consequently enter a new status of being a patient.[68-70] Until now, such problems mostly have been restricted to findings of high levels of established risk factor levels. This situation changed due to the introduction of examination methods which are able to reveal precursors of clinical disease.

We had the general impression that participants in the carotid ultrasound study did not have negative experiences associated with the screening. None of those who were informed that they had plaque later took contact with the medical staff involved in the survey due to anxiety or concern about suspected disease. Nor did we get any negative response from general practitioners. Those who might have been most concerned by the findings at the carotid ultrasound screening were those participants in whom carotid stenosis was found. In the group of 248 subjects with suspected stenosis, 232 later have been followed with annual ultrasound and clinical examination. After two years of follow-up, two of the participants did not want to have further examinations. One of them underlined that the reason was not

unwillingness or lack of motivation, but long distance from the homeplace and concomitant serious illness. The other did not tell why she wanted to quit.

We have not systematically evaluated how a diagnosis of stenosis may have influenced the quality of life for the participants. However, they have expressed gratitude and satisfaction for being followed up. One of the participants has, however, expressed anxiety and concern for more serious disease, specifically stroke, because of the incidental finding of stenosis. This patient has been offered a "low-threshold" possibility to contact the neurologists for consultation or examination whenever she feels a need for that.

However, there is a need for scrutinizing such negative effects of screening. Such a study is ongoing at our institute.

In population-based studies, it is important to obtain a high participation rate to reduce information and selection biases. Advertising in media to increase the public response often focus on health benefit for the participants by screening on risk factors/diseases. It was therefore interesting to note that many of the study participants explicitly stated that they would never have met if the only reason for participation had been evaluation of their own risk factor status or diagnosing any asymptomatic illness. Their main motivation for attending the survey was to contribute to scientific research.

In general, most people might well be aware of "the pros and contras" of a research-motivated health survey, and are probably not "misled" into participation in such studies. May be we are worrying too much about the potential negative side effects of screening populations?

6. IMPLICATIONS FOR CLINICAL PRACTICE AND FURTHER RESEARCH

This study shows that having a stenotic carotid plaque is a strong risk factor for mortality. The role of plaque morphology as an independent predictor of clinical disease remains to determine. Should ultrasound examination of the carotid artery be recommended as a screening procedure to identify high risk individuals? It hardly will be any indication for ultrasound in a primary screening context.[71; 72] However, as a part of risk evaluation of high-risk subjects ultrasound screening of the carotid artery may be indicated. Consensus groups have compiled risk tables with risk factors in different combinations to estimate risk for coronary heart disease,[73] and ultrasound assessed carotid atherosclerosis may represent a risk factor adding information in this context. Hypothetically, the finding of a soft plaque in a

young subject with a familial history of coronary disease, may provide indication for cholesterol-lowering drugs, even in the absence of high values of total or LDL cholesterol.

Scepticism has been expressed about surgery on asymptomatic carotid stenosis,[74] and it has been asked for additional criteria to target the operation on those who have most to gain.[75] Only randomised clinical trials may confirm whether plaque echogenicity can be utilized (in addition to degree of stenosis) to pick out those persons who are most likely to benefit.

The great number of observations of different ultrasound variables collected in the fourth survey of the Tromsø Study offers numerous possible approaches to further epidemiologic and clinical cardiovascular research. A study of genetics and carotid atherosclerosis is ongoing. The same are studies of the association between carotid atherosclerosis and morphology and findings at magnetic resonance imaging (MRI) (silent cerebral infarctions, atrophy, and leukoaraiosis), neuropsychological functioning, mood disorders, chlamydia infections, and coagulation factors and vascular endothelium dysfunction. Prospective studies of carotid atherosclerosis as detected in 1994/1995 as predictors of clinical endpoints may be of special interest.

Likewise, if plaque morphology seems to be unchanged by follow-up tracking studies, the interesting hypothesis of a systemic and individual predisposition to specific morphological characteristics[61] may be strengthened. A possible clinical consequence may be that subjects who once have got identified low-echogenic, "soft" plaques are at a continuously higher risk for acute coronary syndromes or ischemic cerebral strokes.

The ultrasound instruments at our laboratory are technically equipped to perform examinations which enable us to extend the ultrasound research to methods yielding functional and dynamic information of vessel wall pathophysiology and thromboembolic events. These two dynamic methods are: 1) estimation of vessel wall function or dysfunction by measuring changes in the diameter of arteries in response to various stimuli,[76] and 2) detection of cerebral microemboli by transcranial Doppler monitoring.[77] The former method is suitable both in epidemiologic and clinical research, the latter more relevant in clinical research.

Endothelium-derived relaxing factor (EDRF) (nitric oxide) is one of many factors determining alterations in vasomotor tone causing variation of the arterial diameter. Such variations in diameter can be measured by B-mode ultrasound with high reproducibility. Because endothelial-derived vessel wall dysfunction in atherosclerosis-free arteries is believed

to be associated with various cardiovascular risk factors and a precursor of atherosclerosis,[78] [79] [80-84] and possibly a phenomenon detectable before irreversible structural damages of vessels have occurred, the ability of measuring impairment of diameter variations may become of importance in future basic and clinical research on atherosclerosis.

In recent years, ultrasound methods have been developed that has enabled detection of microemboli in the cerebral arterial circulation by transcranial Doppler (TCD) monitoring. This is a method that may be an interesting tool for identifying subjects at high risk of cerebral stroke in follow-up studies of our population. Studies have shown that there is an association between symptomatic and asymptomatic carotis stenosis[85] and plaque morphology (in terms of ulceration and lumen thrombus)[32] and number of microemboli by TCD. This method may be of particular interest in exploring any relation between plaque echogenicity and heterogeneity and risk of cerebral emboli.

7. CONCLUSION

The most important conclusions of the present work are the following:

Occurrence and size of ultrasound assessed carotid plaques can be determined in a general population with satisfactory reproducibility for use in epidemiologic and clinical scientific studies but hardly on an individual level with regard to progression/regression of plaques. Agreement in the classification of plaque morphology is also found satisfactory.

There is a sex difference in prevalence of carotid atherosclerosis. The male predominance in atherosclerosis increases until the age of 50 and thereafter declines. Men have softer plaques than women.

Female reproductive factors such as menopause, age at menopause, and hormone replacement therapy in postmenopausal women are significantly associated with carotid atherosclerosis.

Asymptomatic carotid stenosis as detected in a general population is a strong and an independent predictor of death.

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PAPER I

Reproducibility of Ultrasound Assessment of Carotid Plaque Occurrence, Thickness, and Morphology

The Tromsø Study

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Background and Purpose Ultrasonography is increasingly used in vascular research, but there is limited information about the reproducibility of the ultrasound method for screening purposes. In this study the reproducibility of ultrasound assessment of carotid plaque occurrence, thickness, and morphology was examined within the setting of a population health survey.

Methods In 1994/1995, 6720 participants in the Tromsø Study, Norway, underwent B-mode ultrasound scanning of the right carotid artery. The between- and within-sonographer reproducibility of ultrasound assessment of plaque occurrence and thickness was estimated by repeated scanning of a random sample of 107 participants. The between- and within-sonographer reproducibility of plaque morphology classification (echogenicity, four categories and heterogeneity, two categories) was determined by repeated reading of videotaped images of 119 randomly selected arteries with plaques.

Results Between- and within-sonographer agreement on plaque occurrence was substantial with κ values (95% CI) of 0.72 (0.60 to 0.84) and 0.76 (0.63 to 0.89), respectively. Reproducibility of plaque thickness measurements was moderate, with mean absolute differences ranging between 0.25 and 0.55 mm (coefficients of variation between 13.8% and 22.4%). Agreement on plaque morphology classification was high, with κ values ranging between 0.54 and 0.73.

Conclusions Population screening using B-mode ultrasound provides a valuable means for the detection and morphological evaluation of carotid plaques, whereas measurements of plaque thickness are subject to considerable measurement error. (***Stroke*. 1997;28:2201-2207.**)

Key Words • atherosclerosis • carotid arteries • ultrasonography

Ultrasound-assessed carotid atherosclerosis correlates with atherosclerosis in other arterial territories and is associated with clinical cardiovascular disease.[1,2] Both uniformly increased intima-media thickness and protruding plaques appear to be ultrasound markers of general atherosclerosis, the latter being an expression of more advanced disease and a potential precursor of clinical events. Not only the extent of atherosclerosis but also morphological characteristics of plaques may be evaluated with ultrasound. Lipid-rich plaques, which may be particularly prone to rupture and cause a cardiovascular event, only poorly reflect emitted ultrasound and appear echolucent (dark) and heterogeneous on ultrasound images.[3-6] Studies on selected groups of patients indicate that ultrasound morphology of stenotic carotid plaques is an independent risk factor of stroke,[5,7,8] and plaque composition might therefore affect decision making in reference to carotid endarterectomy in asymptomatic patients. Since recent studies indicate that cardiovascular risk factors correlate with histological plaque characteristics,[5,9] the sonographic appearance of plaques might also be used for in vivo studies of the determinants of atherosclerosis within populations.

The reproducibility of ultrasound carotid intima-media thickness measurements has been examined extensively. Surprisingly, studies on variability among sonographers on carotid plaque detection have not been published, and to our knowledge only two reproducibility studies of ultrasound plaque morphology are reported.[10,11] We therefore examined the reproducibility of ultrasound assessment of carotid plaque occurrence, thickness, and morphology within the setting of a population health screening in Tromsø, Norway.

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Subjects and Methods

Subjects

The Tromsø Study was started in 1974 and is a single-center prospective follow-up study of inhabitants in the municipality of Tromsø, Norway. The primary objective is to investigate determinants of chronic diseases by means of epidemiological, clinical, and basic research to assess etiologic significance and to identify potentially modifiable determinants that may be developed into preventive or therapeutic strategies. The main focus is on cardiovascular diseases. The study design includes repeated population health surveys to which total birth cohorts and random samples are invited.

The fourth survey of the Tromsø population 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 to 12 weeks apart. All inhabitants older than 24 years were invited to the first visit, and 27 161

subjects, 78% of the eligible population, participated. A protocol similar to the previous surveys in this population was followed.[12] The examination included standardized measurements of height, weight, blood pressure, nonfasting serum lipids, serum calcium, γ-glutamyltransferase, hemoglobin and blood cell counts, and a 20-second electrocardiography of lead I. Two questionnaires covered previous and present diseases and symptoms, use of drugs, lifestyle (physical activity, smoking, alcohol intake), dietary habits, and socioeconomic status.

All subjects aged 55 to 74 years and random 5% to 10% samples in the other age groups were invited to the second visit. A total of 6891 subjects, 98% of those who participated in the first visit and were eligible for the second visit, attended. The second visit comprised ultrasonographic examination of the right carotid artery and the abdominal aorta, echocardiography, a 12-lead resting electrocardiogram, a 90-second rhythm electrocardiogram during standardized deep breathing, measurements of bone density, body fat composition, waist and hip circumference, sitting and standing blood pressures, and urine and blood sampling. The study was approved by the regional ethical committee.

Reproducibility of Plaque Occurrence and Plaque Thickness

The reproducibility study was designed to study between-sonographer (different sonographers on the same occasion) and within-sonographer (same sonographers on two separate occasions) agreement on the presence of carotid atherosclerotic plaque in the beginning (first reproducibility study) and the end (second reproducibility study) of the survey period. The subjects were examined by the three same sonographers with an interval of 1 week in the first (weeks 10 and 11) and 3 weeks in the second (weeks 37 and 40) reproducibility study.

The sonographers were blinded to each other's results and to medical information about the participants. One of the sonographers was a neurologist with 10 years of experience in ultrasound examination of the carotid artery, the second was a physician, and the third was a specially trained technician. A 2-month training protocol was completed before the survey started. In addition, the first 200 survey examinations conducted by the physician and the technician were supervised by the neurologist. At the start of the first reproducibility study the physician and the technician had performed approximately 300 and 600 examinations, respectively, on their own.

A total of 111 subjects were invited to the two reproducibility studies. All of them attended, but some of them met on only one occasion, and in a few instances some participants were not examined by all three sonographers. For the between-sonographer study we chose the weeks from the first and second reproducibility studies with the largest number of paired observations. The neurologist did not examine participants in week 40, and data on within-sonographer variability for the neurologist are therefore available only from the first reproducibility study. A total of 107 subjects were included in the analysis. Among these there were 77 subjects who attended the first and 30 subjects who attended the second reproducibility study.

High-resolution B-mode ultrasonography of the right carotid artery was performed with an ultrasound scanner (Acuson Xp10 128 ART [upgraded]) equipped with a linear array 5- to 7-MHz transducer. The subjects were examined in the supine position with the head turned slightly to the left. The common, internal, and external carotid arteries were identified by combining B-mode and color Doppler/pulsed-wave Doppler ultrasound. We attempted to identify and record atherosclerotic plaques from six segments of the carotid artery: the near and far walls of the right internal carotid artery as far upstream from the bifurcation as technically possible, the right carotid bulb of the common carotid artery (the bifurcation segment), and the right common carotid artery from the bifurcation and downstream to the supraclavicular region. Frozen ultrasound images were stored on sVHS videotapes; a 1-minute live recording of the carotid artery from different transducer positions and angles was also stored to obtain a representative recording of plaque thickness and morphology.

Instrument imaging adjustments (preprocession and postprocession, persistence, transmit zones, log compression, image depth, transmit power) were set at fixed values. The gain setting (including the depth gain compensation curve), however, was adjusted according to interindividual differences such as neck thickness, subcutaneous fat, and echogenicity of the near artery wall structures 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. The gain should not be set so high that structure details of the high-echogenic far wall media-adventitia interface are concealed.

A plaque was defined as a localized protrusion of the vessel wall into the lumen. The maximum plaque thickness was measured on-line on frozen B-mode images marked with electronic calipers with measurement readout in tenths of a millimeter. The results were recorded on videotapes and on written forms by the sonographers. In the far wall the plaque thickness was defined as the distance between the lumen-plaque interface and the media-adventitia boundary. Plaques in the near wall were measured from the far edge of periadventitia-adventitia interface to the far edge of the intima-lumen interface.[13] According to the protocol, plaques should be visualized in the full diameter of the vessel; ie, both the proximal and the distal parts of the plaque should be "attached" to the typical double-lined intima-media structure, and the double lines should also be visible on the opposite side of the vessel lumen. The sonographers attempted by gain adjustments and transducer angling to obtain the highest possible echogenicity of the plaques, ie, echo signals as bright as possible without obscuring structural details. Plaque thickness was defined as the single maximum plaque thickness in any of the six measured segments.

Reproducibility of Plaque Morphology Classification

Two of the sonographers performed a separate between-observer reproducibility study on plaque echogenicity and heterogeneity on 119 carotid arteries with plaques. The echogenicity and heterogeneity classification was performed off-line on plaques from one sVHS videotape from the first and one from the second part of the survey period. The two sonographers were blinded for each other's results. To study within-observer variability a second reading was performed by one of the sonographers 5 weeks after the first reading.

Plaque echogenicity was graded from 1 to 4, where grade 1 denotes low echogenicity or echolucency (defined as a plaque appearing black or almost black as flowing blood), and grade 4 denotes strong echogenicity (defined as a plaque appearing white or almost white, similar to the far wall media-adventitia interface) (Fig 1). Plaques that were difficult to classify because of echo-shadowing from calcifications in near wall plaques, calcifications just below the surface of a far wall plaque hiding substantial parts of the rest of the plaque, or unsatisfactory imaging quality were defined as unclassifiable (n=7).

Plaques were also classified according to structural appearance criteria as either heterogeneous or homogeneous (Fig 1). Plaques were characterized as heterogeneous 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 homogeneous. If more than one plaque was present in a carotid artery, an overall echogenicity and heterogeneity score was estimated from the total plaque area following the aforementioned guidelines.

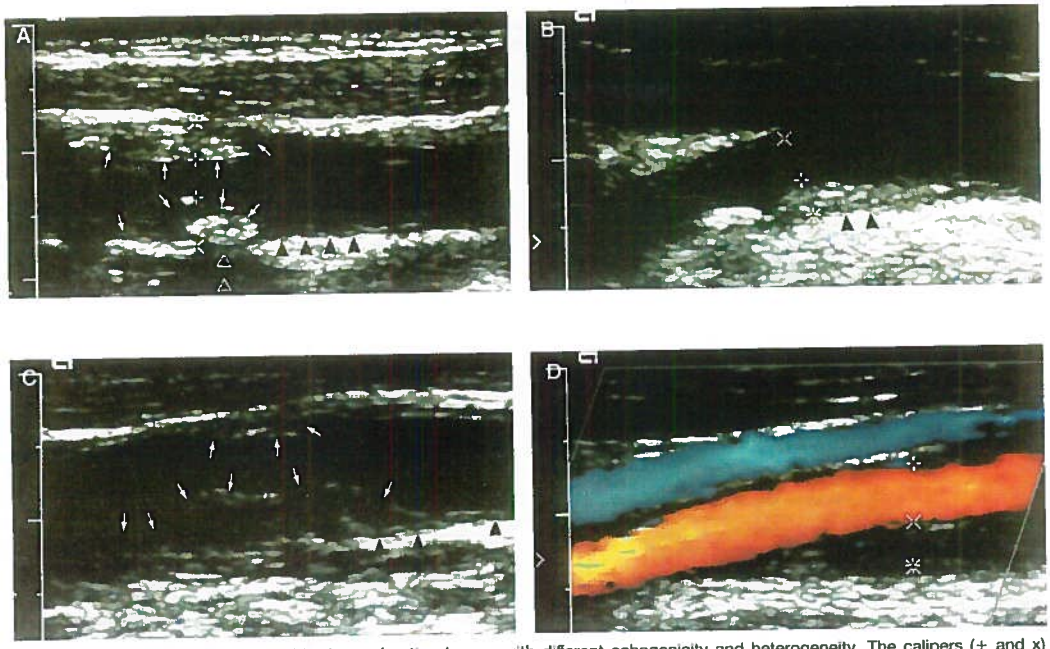

FIG 1. Ultrasound images of carotid atherosclerotic plaques with different echogenicity and heterogeneity. The calipers (+ and x) indicate the artery lumen diameter and plaque thickness. A, Predominantly echogenic (grade 3) and heterogeneous plaque visualized in the near and the far artery walls (white arrows indicate plaque-lumen interface). The far wall plaque is casting an echo shadow (open triangles), hiding the media-adventitia interface underneath. Media-adventitia interface (black arrowheads) to the right of the shadow appears bright and echogenic. B, Predominantly echogenic (grade 3) and homogeneous plaque in the far wall. Media-adventitia interface (black arrowheads) is echogenic. C and D, Images from the same carotid artery (slightly different interrogation angle) showing an echolucent (grade 1) and homogeneous plaque (white arrows) mostly in the far wall, but with a small part of the plaque also visible in the near wall. Color Doppler was used to identify the outlines of echolucent plaques (D).

Statistical Analysis

The between- and within-sonographer variability in the assessment of plaque occurrence, echogenicity, and heterogeneity was analyzed by the use of the kappa statistic (κ). κ measures the agreement that occurs above chance[14] and may have values between -1 (complete disagreement) and $+1$ (perfect agreement). κ values from 0 to 0.20 are categorized as slight agreement, those from 0.21 to 0.40 as fair, those from 0.41 to 0.60 as moderate, those from 0.61 to 0.80 as substantial, and those above 0.80 as almost perfect agreement.[15] The 95% confidence intervals (CIs) were estimated as κ estimates ± 2 SE according to Fleiss.[14] Mean arithmetic differences (95% CI) and mean absolute differences were used to estimate the reproducibility of measurements of plaque thickness. The coefficient of variation (CV) of differences was calculated according to the formula

$$CV = \frac{s}{\bar{x}} \times 100\%$$

The SD of the measurement error (s) was calculated according to the formula $s = SD/\sqrt{2}$. SD is the standard deviation of the arithmetic differences between measurements, and $\bar{x}$ is the mean value of plaque thickness.[16] The arithmetic differences between paired examinations were plotted against their average to examine whether the differences were reasonably constant throughout the range of measurements.[17] 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." 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 $P < .05$ were considered statistically significant. The SAS software package was used.[18]

Results

Table 1 shows that those who took part in the reproducibility study were representative of the total study population. The participants in the reproducibility study were slightly younger than the rest of the study population since very old persons were not invited to the

TABLE 1. Selected Characteristics of the Tromsø Study Population

	Participating in the Reproducibility Study	
Characteristic	**Yes**	**No**
No.	107	6613
Age, y	57.4 (10.7)	60.3 (10.2)*
Male, %	47.8	49.3
Body mass index, kg/m^2	25.7 (3.8)	26.0 (4.0)
Diastolic blood pressure, mm Hg	78.7 (11.8)	80.2 (12.1)
Systolic blood pressure, mm Hg	136.3 (20.5)	140.3 (21.4)
Serum total cholesterol, mmol/L	6.92 (1.44)	6.75 (1.29)
Serum HDL cholesterol, mmol/L	1.59 (0.46)	1.53 (0.44)
Current smoking, %	26.4	33.1
Prevalence of carotid plaque, %	48.6	49.4

Values are mean (SD) or percentage.
*$P < .05$ compared with participants in the reproducibility study.

TABLE 2. Agreement on Occurrence of Carotid Plaques

Sonographer Pair/Sonographer	No. of Subjects	κ	
		Estimate	95% CI
Between-sonographer agreement			
First reproducibility study			
Technician vs physician	76	0.66	0.43-0.89
Neurologist vs technician	75	0.76	0.52-0.99
Physician vs neurologist	75	0.66	0.45-0.87
Second reproducibility study			
Technician vs physician	30	0.94	0.58-1.00
Neurologist vs technician	24	0.63	0.22-1.00
Physician vs neurologist	24	0.74	0.23-1.00
Overall agreement between sonographers	304	0.72	0.60-0.84
Within-sonographer agreement			
First reproducibility study			
Technician	70	0.83	0.59-1.00
Physician	70	0.66	0.42-0.90
Neurologist	61	0.84	0.58-1.00
Second reproducibility study*			
Technician	24	0.54	0.14-0.94
Physician	24	0.92	0.50-1.00
Overall agreement within sonographers	249	0.76	0.63-0.89

CI indicates confidence interval.
*The neurologist did not participate.

reproducibility study because it was strenuous and time-consuming. About 49% of the participants had one or more atherosclerotic plaques (Table 1).

Plaque Occurrence

Overall between-sonographer agreement on the presence of atherosclerotic plaques showed a κ value of 0.72 (95% CI, 0.60 to 0.84), indicating substantial agreement (Table 2) There was no significant difference in the agreement between the first and the second reproducibility study. Within-sonographer agreement on plaque occurrence was slightly better than between-sonographer agreement with an overall κ of 0.76 (95% CI, 0.63 to 0.89) (Table 2). Reproducibility of plaque detection did not differ significantly among the three sonographers.

Plaque Thickness

Between-sonographer reproducibility of plaque thickness is summarized in Table 3. The mean arithmetic differences were generally small, ranging from 3% to 12% of mean plaque thickness. The physician tended to measure plaques thinner than the technician and the neurologist. The mean absolute differences varied between 0.25 and 0.55 mm, and the CVs were between 17.9% and 22.4%. The limits of agreement were ±1.04, ±1.27, and ±1.32 mm for comparisons of the technician versus the physician, the neurologist versus the technician, and the physician versus the neurologist, respectively. Fig 2 shows that between-sonographer variability is greater with increasing plaque thickness.

Within-sonographer reproducibility of plaque thickness is shown in Table 3. The reproducibility was similar for the three sonographers and was better than the between-sonographer reproducibility. The within-sonographer variability was greater with increasing plaque thickness (Fig 2).

Plaque Morphology

Between- and within-sonographer agreement on plaque echogenicity classification was substantial (Table 4). When echogenicity grades 1 and 2 were merged into one low-echogenicity category and grades 3 and 4 were merged into one high-echogenicity category, the κ values for between- and within-sonographer variability were 0.80 (95% CI, 0.61 to 0.99) and 0.79 (95% CI, 0.61 to 0.97), respectively. Between- and within-sonographer agreement on plaque heterogeneity classification showed κ values of 0.71 (95% CI, 0.52 to 0.90) and 0.54 (95% CI, 0.36 to 0.72), respectively (Table 4).

TABLE 3. Reproducibility of Measurements of Maximum Plaque Thickness*

Sonographer Pair/Sonographer	No. of Subjects	Mean Plaque Thickness, mm	Mean (95% CI) Arithmetic Difference, mm	Mean Absolute Difference, mm	Coefficient of Variation, %	Limits of Agreement, mm
Between-sonographer reproducibility						
Technician vs physician	41	2.09	0.19 (0.37, 0.01)	0.25	17.9	±1.04
Neurologist vs technician	40	2.17	0.06 (−0.14, 0.26)	0.42	21.2	±1.27
Physician vs neurologist	37	2.13	−0.26 (−0.03, −0.49)	0.55	22.4	±1.32
Within-sonographer reproducibility						
Technician	42	2.15	−0.02 (−0.15, 0.11)	0.31	13.8	±0.82
Physician	40	1.96	0.07 (−0.05, 0.19)	0.28	13.7	±0.75
Neurologist	27	2.33	−0.01 (−0.19, 0.17)	0.36	15.1	±0.97

*Pooled data from the first and the second reproducibility studies.

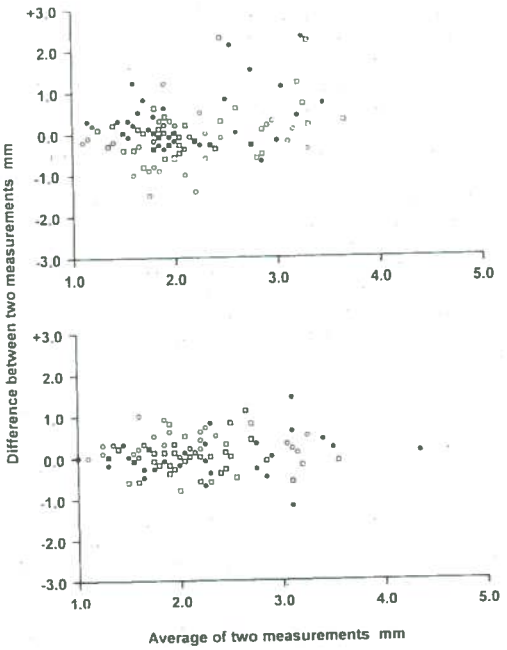

FIG 2. Plots of reproducibility of ultrasound measurements of carotid artery plaques. Top panel shows difference against the average of measurements by two sonographers on one occasion. Bottom panel shows difference against average of measurements by one sonographer on two occasions. Open and filled circles and open squares represent three different pairs of sonographers (upper panel) and three different sonographers (lower panel).

Discussion

Ultrasound is increasingly used as a noninvasive method in basic and clinical research. The reproducibility of echographic measurements of carotid artery intima-media thickness is well established,[19-24] but the reliability of ultrasound plaque detection and morphological classification has been studied less well. The present results show that ultrasound can be used both to identify and to classify carotid plaques with an acceptable degree of between- and within-sonographer reliability. Measurements of plaque thickness, however, are subject to considerable measurement error. To enhance the generalizibility of the results we examined a random sample of participants in a population health survey, and we did not exclude subjects on the basis of ultrasonographic, demographic, or medical characteristics.

The dependence of B-mode image quality on interrogation angle and fine adjustment of instrument controls makes the role of the sonographer crucial to the measurement process. Previous reproducibility studies on plaque detection were based on multiple off-line readings of single vessel-wall images recorded on videotape,[20,25] thus bypassing the influence of the sonographer on measurement variability. Although the present study demonstrates a substantial overall agreement on the presence of plaques, a number of plaques could not be identified on repeated examinations. What are the characteristics of such plaques?

We identified two factors influencing agreement, plaque localization, and plaque size. Agreement on the occurrence of near wall plaques was significantly lower than of far wall plaques: complete agreement among all three sonographers on the presence of a plaque was found in 61% of those near wall plaques that were identified by any of the sonographers, whereas complete agreement was found in 82% of the far wall plaques ($\chi^2_{df=1}=4.46$; $P=.035$). Higher variability of detection was also observed for smaller plaques: the mean (SEM) thickness of plaques detected by only one or two of the three sonographers was 1.58 (0.07) mm, whereas the mean thickness of those plaques detected by all sonographers was 2.42 (0.09) mm ($P<.001$). Our study was conducted within the setting of a population health survey, and each scanning was scheduled to be completed within approximately 20 minutes. It is possible that the available time was not sufficient for scrutinizing near wall structures, which apparently are more difficult to identify than far wall structures. Furthermore, it may often be difficult to decide whether a minor wall irregularity represents a plaque or only "wall roughness." We defined a plaque as a "localized protrusion of the vessel wall into the lumen." The results might have improved by specifying in the protocol that the qualifying lesion was a distinct area with an intima-media thickness more than 50% thicker than neighboring sites judged visually.[26] However, this definition might have excluded a significant proportion of early lesions from being identified. There were no notable differences between the results obtained in the first and the second reproducibility studies, indicating that presurvey training of sonographers and standardization of the procedures were sufficient.

The present study indicates that plaque thickness can be measured without systematic differences (bias) among sonographers. There is, however, much room for improvement regarding the precision of such measurements: the limits of agreement (Table 3) indicate that even a 60% change in an individual's plaque thickness may be attributable to measurement error if the measurements are performed by different sonographers. The corresponding percentage for repeated measurements by a single sonographer is 40%, illustrating that within-sonographer variability was considerably lower than between-sonographer variability. Clinical studies on selected groups of patients have found mean absolute

TABLE 4. Agreement on Classification of Plaque Echogenicity and Heterogeneity

	Between-Sonographer Agreement		Within-Sonographer Agreement	
Plaque Characteristics	No. of Plaques	κ (95% CI)	No. of Plaques	κ (95% CI)
Echogenicity	116	0.73 (0.59, 0.87)	111	0.69 (0.55, 0.83)
Heterogeneity	112	0.71 (0.52, 0.90)	109	0.54 (0.36, 0.72)

CI indicates confidence interval.

differences between sonographers ranging between 0.31 and 0.36 mm (reader variability not included),[19,21] which are similar to our findings, whereas a greater difference (0.63 mm) was reported from a population-based study.[24] These results indicate that ultrasound may not be used for monitoring the progression/regression of plaque thickness on an individual level. Our data suggest that sample size requirements for clinical trials will vary considerably depending on whether the ultrasound measurements are conducted by a single or by several sonographers: a single sonographer may detect a 10% difference (0.20 mm) in plaque thickness at $P=.05$ with a power of 0.90 with a total study size of 150 subjects (for a two-sample comparison), whereas approximately 400 subjects are required if the measurements are done by several sonographers. The reproducibility of the thickness measurements might improve by having a fixed and known angle of interrogation and by using the average of values obtained on separate occasions.

The usefulness of plaque thickness measurements in epidemiological studies may be limited because plaques available for quantitative measurements are present in only a proportion of the population. Reproducible measurements of intima-media thickness in the carotid artery are achievable in most subjects,[27] but a thick intima-media may not always reflect early atherosclerosis.[28,29] One of the outstanding issues to be resolved in atherogenesis is which mechanisms and risk factors are associated with the evolution of a uniform wall thickening into an atherosclerotic plaque.[30] This requires prospective studies with baseline and follow-up data on both intima-media thickness and plaque occurrence.

High-resolution ultrasound allows morphological characterization of the carotid artery plaque that matches reasonably well with histological features of specimens from endarterectomies[4,5,31] or from autopsy.[4,32] Plaques that only poorly reflect emitted ultrasound (echolucent) have a high content of lipid and/or hemorrhage, whereas plaques that strongly reflect ultrasound (echogenic) have a higher content of dense fibrous tissue and calcified material. Carotid plaque composition analyzed by ultrasound correlates with cardiovascular risk factor levels,[10] and some reports,[5-8,33,34] but not all,[35,36] have found an association between the morphology of stenotic plaques and the risk of stroke. There is, however, no consensus on ultrasonographic criteria for morphological characterization of carotid plaques. It is important to standardize echogenicity classification against defined and well-recognized reference structures located adjacent to the plaque. Because such classifications are based on subjective judgment, it has been suggested to use densitometric evaluation or radiofreqency-based tissue characterization.[3,37] Such methods provide more objective and quantitative measures on plaque morphology, but they are time-consuming and not practical for use in epidemiological studies. In the present study the two ultrasound reference structures used as extremes on a gray scale were the almost nonreflecting flowing blood (echolucent, grade 1) on the one side and the bright, high-echogenic far wall media-adventitia interface (echo-rich, grade 4) on the other side (Fig 1). It has been suggested that the mastoid muscle and the cervical vertebra may be used as reference structures.[38] The usefulness of those structures is not documented, to our knowledge, and it may be suggested that reference structures that are located close to the plaque should be preferred compared with more remote structures. The deeply localized vertebrae may not always give rise to high-reflecting echoes, possibly because of scarce remaining ultrasound energy after passage of the high-frequency ultrasound signals through the tissues in the neck. Lack of adequate reference structures is probably a major source of error in studies evaluating ultrasound morphology. In the present study we obtained an acceptable agreement on the classification of carotid plaques in terms of echogenicity and heterogeneity. Grønholdt et al[10] and Geroulakos et al[11] have previously reported similar κ values (0.61 and 0.79, respectively) for interobserver agreement on echogenicity classification on stenotic carotid plaques. No reference structures were used in those studies.

Although the agreement on plaque morphology was acceptable in the present study, several plaques were differently classified on repeated examinations. There was no association between disagreement of echogenicity scoring and plaque size or plaque localization (data not shown). Disagreement on heterogeneity classification was, however, associated with lower plaque echogenicity (grades 1 and 2) ($\chi^2_{df=1}=10.1$; $P=.002$) but was not associated with plaque localization or size. The reason may be that some echogenic plaques containing echo-poor areas caused by shadows from calcium deposits were scored as heterogeneous instead of either homogeneous or unclassifiable.

Lipid-rich atherosclerotic plaques in the coronary arteries are particularly vulnerable for rupture and are associated with higher risk of myocardial infarction and death than fibrocalcified plaques.[39] There are, however, currently no sensitive and practical means of detecting vulnerable coronary plaques in vivo. If carotid and coronary artery plaques share common morphological characteristics within individuals, then ultrasound of the carotid artery may be a simple, noninvasive test to screen asymptomatic subjects at high risk of cardiovascular events.

In conclusion, reproducible ultrasound measurements of carotid plaque occurrence and plaque morphology may be achieved within the setting of a population health survey. Variability of plaque thickness measurements is considerably greater between than within sonographers and is also dependent on plaque thickness. Further studies are needed to clarify whether ultrasound plaque morphology reflects different stages in atherogenesis or different influences on the development of atherosclerosis and whether carotid and coronary plaques share common histological characteristics within individuals. We are currently conducting a population-based prospective follow-up study to assess whether ultrasound plaque morphology predicts the risk of cerebrovascular and cardiovascular morbidity and mortality.

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PAPER II

Age and Sex Differences in the Distribution and Ultrasound Morphology of Carotid Atherosclerosis

The Tromsø Study

Oddmund Joakimsen, Kaare H. Bønaa, Eva Stensland-Bugge, Bjarne Koster Jacobsen

Abstract—Atherosclerosis begins early in life and is the major underlying cause of cardiovascular morbidity and death. Yet, population-based information on age and sex differences in the extent and morphology of atherosclerosis throughout life is scarce. Carotid atherosclerosis can be visualized with B-mode ultrasound and is a marker of atherosclerosis elsewhere in the circulation. We assessed both the prevalence and the morphology of carotid atherosclerosis by B-mode ultrasound in 3016 men and 3404 women, 25 to 84 years old, who participated in a population health survey. The participation rate was 88%. Plaque morphology was graded according to whether a plaque was predominantly soft (echolucent) or hard (echogenic). Atherosclerotic plaques were found in 55.4% of the men and 45.8% of the women. In men, there was a linear increase with age in the prevalence of carotid atherosclerosis, whereas in women, there was a curvilinear age trend, with an inflection in the prevalence rate of women at ≈50 years of age. The male predominance in atherosclerosis declined after the age of 50 years, the plaque prevalence being similar in elderly men and women. Men had softer plaques than women; this sex difference in plaque morphology increased significantly (P=0.005) with age. The sex difference in the prevalence of atherosclerosis and the female age trend in atherosclerosis show significant changes at the age of ≈50 years, suggesting an adverse effect of menopause on atherosclerosis. The higher proportion of soft plaques in men compared with women increases with age and may partly account for the prevailing male excess risk of coronary heart disease in the elderly despite a similar prevalence of atherosclerosis in elderly men and women. (***Arterioscler Thromb Vasc Biol.* 1999;19:3007-3013.)**

Key Words: ultrasonography ■ carotid arteries ■ atherosclerosis ■ sex

High-resolution B-mode ultrasound is a valid and reproducible method to visualize and quantify carotid atherosclerosis noninvasively. Both ultrasound and autopsy studies have found that carotid atherosclerosis correlates well with atherosclerosis elsewhere in the circulation and can be used as a marker of general atherosclerosis.[1–4] Previous population-based studies on ultrasound-detected atherosclerosis are small or did not examine sex differences in the prevalence and extent of atherosclerosis from young adulthood through old age.[5–9]

Not only the extent but also the morphology of atherosclerosis is important for the development of clinical vascular disease. Soft and lipid-rich plaques in the coronary arteries seem to be particularly prone to rupture and cause occlusive thrombosis and acute coronary syndromes,[10] and ultrasound morphology of stenotic carotid plaque is an independent risk factor for stroke.[11,12] Dark and low-echogenicity (echolucent) plaques on ultrasound correspond with soft and lipid-rich plaques at autopsy, supporting the validity of the ultrasound method.[13–15] The reproducibility of carotid plaque morphology is acceptable.[16] No studies on age and sex differences in ultrasound-assessed plaque morphology have been published.

In this population-based ultrasound study, we examined the prevalence and morphology of carotid atherosclerosis in 6420 men and women 25 to 84 years old.

Methods

Subjects

The Tromsø Study was started in 1974 and is a single-center study of inhabitants in the municipality of Tromsø, Norway. The aims of the study are to investigate, by means of epidemiological and clinical research, determinants of chronic diseases to assess etiological significance and to identify potentially modifiable determinants that may be developed into preventive or therapeutic strategies. The main focus is on cardiovascular diseases. The study design includes repeated population health surveys to which total birth cohorts and random samples of other age groups are invited.

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 2 screening visits 4 to 12 weeks apart. All inhabitants >24 years old were invited to the first visit, and all subjects 55 to 74 years old and random 5% to 10% samples in the other 5-year age groups >24 years old were invited to both visits. A total of 6891 subjects, 88% of the eligible population, attended both visits. The protocol for the first visit was similar to the previous surveys in this population[17] and included standardized measurements

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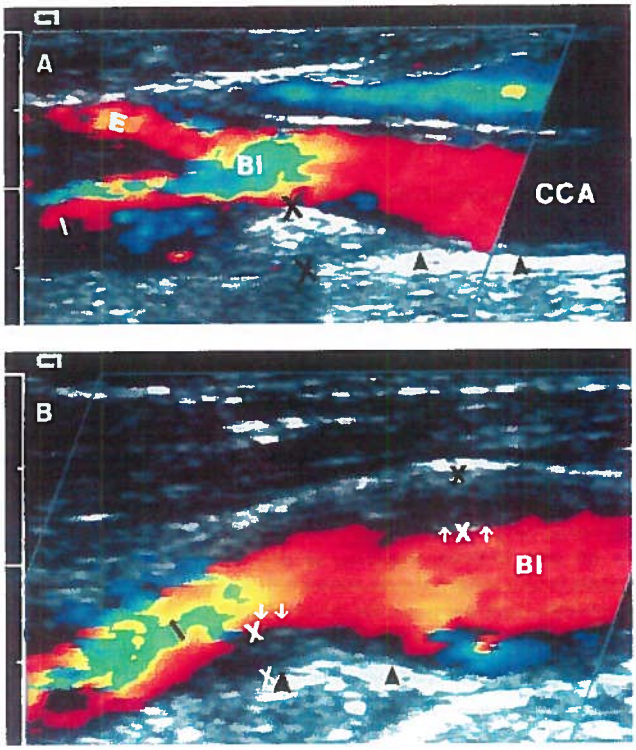

Figure 1. Ultrasound images of carotid atherosclerotic plaques with different echogenicity. The calipers X indicate plaque thickness; I, internal carotid artery; E, external carotid artery; BI, carotid bifurcation; and CCA, common carotid artery. The reference structure for the grading of echogenicity (the media-adventitia interface indicated by black arrowheads) appears bright and echogenic. A, A predominantly echogenic (grade 3) plaque located in the far wall of the carotid bifurcation. B, Two predominantly echolucent (grade 2) plaques, one in the far wall of the internal carotid artery and the other in the near wall of the carotid bifurcation. Color Doppler was used to identify the plaque-lumen interface.

of height, weight, blood pressure, and nonfasting serum lipids. The second visit also included ultrasonographic examination of the right carotid artery.[16] The study was approved by the regional ethical committee.

Cardiovascular Risk Factors

Height and weight were measured with the subject in light clothing without shoes; body mass index was calculated as weight divided by the square of height (kg/m^2). The letter of invitation gave information about the survey and also included questions on previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (all yes/no), treated hypertension (never/previously/currently), and smoking habits. The questionnaire was checked for logical inconsistencies.

Ultrasonography

High-resolution B-mode ultrasonography of the right carotid artery was performed on 6420 persons with an ultrasound scanner (Acuson Xp10 128 ART-upgraded) equipped with a linear-array 5-MHz color Doppler/pulsed-wave Doppler and 7-MHz B-mode transducer. The subjects were examined in the supine position with the head turned slightly to the left. The common, internal, and external carotid arteries were identified by combined B-mode and color Doppler/pulsed-wave Doppler ultrasound. We attempted to identify and record atherosclerotic plaques from 6 sites of the carotid artery: the near and far walls of the internal carotid artery as far upstream as technically possible; the bifurcation of the common carotid artery, ie, the distal part of the common carotid artery from the point at which the 2 parallel near and far walls start to deviate, up to the tip of the flow divider that separates the external carotid artery from the internal carotid artery; and the common carotid artery from the bifurcation segment and as far downstream of the supraclavicular region as technically possible. Frozen ultrasound images were stored on sVHS videotapes, and a 1-minute live recording of the carotid artery from different transducer positions and angles was also stored to document representative recordings of plaque thickness and morphology.

Instrument imaging adjustments (preprocession and postprocession, persistence, transmit zones, log compression, image depth, transmit power) were set at fixed values. The gain setting (including the depth gain compensation curve), however, was adjusted according to such factors as neck thickness, subcutaneous fat, and echogenicity of the near artery wall structures to obtain optimal visualization of arterial wall morphology. The gain setting was also changed continuously during the scanning procedure on the same individual to enhance plaque detection and characterization. The gain was not set so high that structural details of the high-echogenicity far-wall media-adventitia interface were concealed.

A plaque was defined as a localized protrusion of the vessel wall into the lumen. The maximum plaque thickness was measured online on frozen B-mode images marked with electronic calipers with measurement readout in tenths of a millimeter. The measures were recorded on videotapes and on written forms by the sonographers. In the far wall, the plaque thickness was defined as the distance between the lumen-plaque interface and the media-adventitia interface. Plaques in the near wall were measured from the far edge of the periadventitia-adventitia interface to the far edge of the intima-lumen interface.[18] According to the protocol, plaques were to be visualized in the full diameter of the vessel, ie, both the proximal and the distal parts of the plaque should be "attached" to the typical double-lined intima-media structure, and the double lines should also be visible on the opposite wall of the vessel lumen. Focal calcification within the vessel wall (causing echo shadowing distally) without protrusion into the lumen was not considered to indicate atherosclerotic lesions.[19]

Plaque morphology, in terms of ultrasound echogenicity, was graded from 1 to 4, where grade 1 denotes low echogenicity, or echolucency (defined as a plaque appearing black or almost black, like flowing blood), and grade 4 denotes strong echogenicity (defined as a plaque appearing white or almost white, similar to the far-wall highly echogenic media-adventitia interface) (Figure 1). In

TABLE 1. Selected Characteristics of Subjects Examined by Carotid Ultrasound

Characteristic	Male	Female
No. of subjects	3016	3404
Age, y	61.4 (9.8)	61.3 (10.3)
Prevalence of carotid plaque, %	55.4	45.8
Body mass index, kg/m²	26.0 (3.4)	26.0 (4.5)
Current smoking, %	31.7	31.0
Systolic blood pressure, mm Hg	140.3 (18.9)	139.6 (22.4)
Diastolic blood pressure, mm Hg	81.1 (11.0)	78.1 (11.7)
Serum total cholesterol, mmol/L	6.49 (1.19)	6.92 (1.31)
Serum HDL-cholesterol, mmol/L	1.41 (0.40)	1.66 (0.42)
Serum triglycerides, mmol/L	1.77 (1.12)	1.52 (0.85)
Serum fibrinogen, g/L	3.36 (0.90)	3.45 (0.81)
Treated hypertension, %	14.4	13.8
Diabetes mellitus, %	3.5	3.2

The values are means (SD) or percent.

the analysis, plaques of echogenicity grades 1 and 2 were defined as soft, echolucent plaques, and plaques of grades 3 and 4 were defined as hard, echogenic plaques. Some plaques were difficult to classify because of echo shadowing from calcifications within the plaque hiding the deeper portions of the same plaque or calcium deposits in near-wall plaques casting shadows over the vessel lumen and far-wall plaques. Those plaques were defined as unclassifiable. Unsatisfactory imaging quality from other causes also led to this definition.

We have previously reported the reproducibility of the present ultrasound method.[16] The between- and within-sonographer agreement on plaque occurrence was substantial, with κ values (95% CI) of 0.72 (0.60 to 0.84) and 0.76 (0.63 to 0.89), respectively. Agreement on classification of plaque echogenicity in the 2 categories used in the analysis was also substantial, with κ values (95% CI) of 0.80 (0.61 to 0.99) and 0.79 (0.61 to 0.97) between and within sonographers, respectively.[16] A κ value of 0 means no agreement beyond chance, and a κ value of 1 means total agreement.

Statistical Analysis

Means were compared by 2-sample Student's t test. Logistic regression was used to calculate age-adjusted odds ratios of having soft plaques according to sex and age. Descriptive statistics, t tests, and regression analyses were performed with the SAS software package.[20] The probability values are 2-sided, and a value of $P<0.05$ was considered statistically significant.

Results

Selected characteristics of the 3016 men and 3404 women are presented in Table 1. Men were slightly younger than women and had a higher prevalence of carotid plaque ($P<0.001$). Approximately 32% of both men and women were smoking cigarettes daily. The mean cholesterol level was relatively high, females having significantly higher levels than men ($P<0.001$).

A total of 1670 men (55.4%) and 1558 women (45.8%) had carotid plaques. The prevalence of plaque increased with age in both men and women (Table 2). The age-adjusted odds ratios (95% CI) for plaque prevalence in men compared with women were 1.85 (1.24, 2.76), 1.65 (1.41, 1.91), 1.46 (1.24, 1.73), 0.76 (0.38, 1.55), and 1.56 (1.41, 1.74) among subjects <55 years old, 55 to 64 years, 65 to 74 years, >74 years, and for all subjects, respectively. The odds ratios did not change notably with control for age, body mass index, total cholesterol, HDL cholesterol, current smoking, treated hypertension, and diabetes mellitus: 1.77 (1.10, 2.84), 1.70 (1.44,

TABLE 2. Plaque Prevalence, Mean Number of Plaques Among Subjects With Plaques, Mean Plaque Thickness, and Plaque Localization in the Carotid Artery by Age and Sex

Sex/Age, y	No. of Subjects Examined	Percentage (No.) With Plaque	Mean No. of Plaques*	Mean Plaque Thickness, mm†	Percentages of Subjects With Plaques in Different Locations of the Carotid Artery					
					FWI	NWI	FWB	NWB	FWC	NWC
Male										
25–34	99	3.0 (3)	1.0	1.1	0	0	3.0	0	0	0
35–44	114	14.9 (17)	1.2	1.6	0	0	14.9	1.8	0	0
45–54	150	32.0 (48)	1.3	1.9	9.3	2.0	20.0	9.3	0	2.0
55–64	1422	52.2 (742)	1.5	2.1	14.3	5.2	40.4	15.3	3.2	1.7
65–74	1146	69.4 (795)	1.9	2.3	26.0	10.5	51.9	28.8	8.2	4.2
75–84	85	76.5 (65)	2.1	2.5	25.9	15.3	64.7	37.7	12.9	5.9
Total	3016	55.4 (1670)	1.7	2.2	17.0	6.4	40.3	18.8	4.6	2.5
Female										
25–34	118	1.7 (2)	1.0	1.1	0	0	1.7	0	0	0
35–44	166	10.8 (18)	1.1	1.5	0.6	0	9.0	1.2	0.6	0
45–54	198	18.2 (36)	1.1	1.6	2.5	0.5	12.6	3.0	0.5	0.5
55–64	1453	40.3 (586)	1.3	1.9	9.2	2.8	29.7	10.3	0.8	1.2
65–74	1368	61.0 (834)	1.6	2.1	20.5	7.3	41.7	21.4	3.1	3.1
75–84	101	81.2 (82)	1.8	2.2	31.7	12.9	56.4	32.7	6.9	3.0
Total	3404	45.8 (1558)	1.5	2.0	13.3	4.5	32.3	14.2	1.9	1.9

FWI indicates far wall of internal carotid artery; NWI, near wall of internal carotid artery; FWB, far wall of the bifurcation part of the common carotid artery; NWB, near wall of the bifurcation part of the common carotid artery; FWC, far wall of common carotid artery; and NWC, near wall of common carotid artery.

*Among persons who had ≥1 plaques in the carotid artery (n=1670 men and n=1558 women).

†The mean value of the thickest plaque when >1 plaque was present.

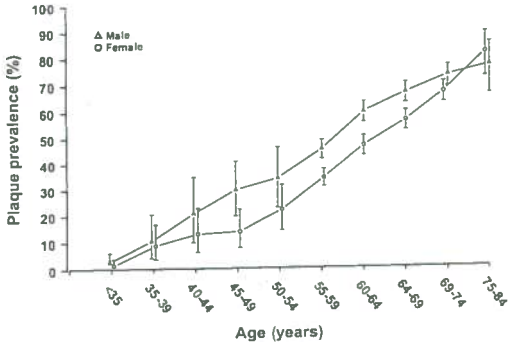

Figure 2. Prevalence of carotid atherosclerosis by age and sex. The vertical bars denote the 95% confidence intervals of proportions.

2.00), 1.59 (1.32, 1.91), 0.87 (0.37, 1.22), and 1.66 (1.47, 1.86) among the same subject groups, respectively. In men, there was a nearly linear increase until the age of 65 years; thereafter, the age-related increase leveled off (Figure 2). Compared with men, women had a less steep increase in plaque prevalence between the ages of 35 and 49 years. After this age, atherosclerosis accelerated more rapidly in women than in men. In the age group of 75 to 84 years, more women (81.2%) than men (76.5%) had carotid atherosclerosis. The difference, however, was not statistically significant. The male-to-female ratio of plaque prevalence was highest in the age group of 45 to 49 years (Figure 3) and declined thereafter. Table 2 also shows that the number of atherosclerotic lesions and the thickness of plaques increased with age in both sexes. The predilection site of atherosclerosis seems to be in the bifurcation segment of the carotid artery, where the number of plaques is highest for both sexes at any age. Figure 4 shows that only 15% of the plaques were located entirely outside the bifurcation segment. There was no sex difference in the within-artery distribution of carotid atherosclerosis.

Soft carotid plaques were present in 37.7% of the 3100 subjects with morphologically classifiable plaques. In all age groups, there was a greater proportion of soft plaques in men than in women (Table 3). The proportion of soft plaques declined with age in both sexes, but more in women than in

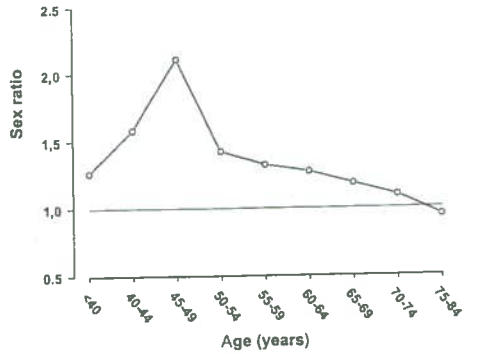

Figure 3. Ratio of male-to-female prevalence of carotid atherosclerosis by age.

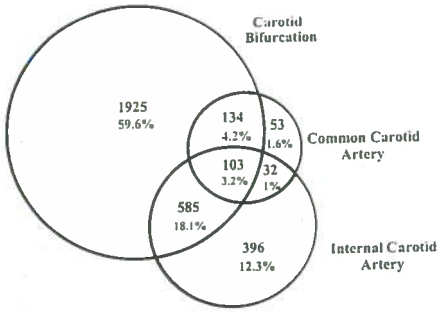

Figure 4. Distribution of plaques among the 3228 participants who had ≥1 carotid plaques.

men; the odds ratio for soft plaques in men compared with women increased by age (Table 3). In a multiple logistic regression analysis with age and sex, there was a statistically significant age-by-sex interaction ($P=0.005$). The prevalence of soft plaques increased with age until 60 years for both sexes (Figure 5). After this age, there was no further increase in prevalence of soft plaques for either sex. In all age groups, more men than women had soft plaques. This sex difference in soft plaque prevalence remained fairly constant from the age of 40 years and throughout old age (Figure 5). The odds ratios did not change notably with control for age, body mass index, total cholesterol, HDL cholesterol, current smoking, treated hypertension, and diabetes mellitus: 1.17 (0.50, 2.74), 1.00 (0.79, 1.26), 1.35 (1.07, 1.71), 2.26 (0.90, 5.65), and 1.14 (0.97, 1.34) among subjects <55 years old, 55 to 64 years, 65 to 74 years, >74 years, and for all subjects, respectively. The interaction between age and sex was now nonsignificant ($P=0.21$). When the 153 women who had ever used postmenopausal hormone replacement therapy were excluded from the analysis, the risk estimates for plaque prevalence and plaque morphology did not change notably even after adjustment for cardiovascular risk factors (data not shown).

Discussion

This population-based ultrasound study demonstrates a strong relationship between age and prevalence of carotid atherosclerosis in both sexes. Similar findings have been reported from other population-based studies (Table 4), but previous studies were small or did not include subjects throughout a broad age range.[5–9] Differences in study designs, including various ultrasound imaging methods, inclusion criteria, and definition of atherosclerosis, make direct comparisons between studies difficult. However, the prevalence of ultrasound-detected carotid atherosclerosis, with a few exceptions, seems to be fairly similar in studies from Europe and the United States (Table 4).

Atherosclerosis occurs more frequently in men than in women. The present study shows, however, that the sex gap in plaque prevalence is strongly influenced by age. The male-to-female ratio in prevalence peaks at age 45 to 49 years and then declines steadily (Figure 2). For subjects >75 years old, the total plaque prevalences in men and women do not differ. The curvilinear shape of the atherosclerosis prevalence curve for women suggests that the incidence of new athero-

TABLE 3. Proportion of Soft Plaques in Subjects With Carotid Plaques According to Age and Sex, and Age-Adjusted Odds Ratios for Soft Carotid Plaques in Men Compared With Women

	Men		Women		
Age, y	No. With Plaques	Percentage With Soft Plaques	No. With Plaques	Percentage With Soft Plaques	Odds Ratio (95% CI)
<55	67	56.7	53	45.3	1.59 (0.77, 3.30)
55–64	723	43.7	559	42.2	1.06 (0.85, 1.32)
65–74	771	36.3	787	29.4	1.37 (1.11, 1.70)
>75	64	34.4	76	23.7	1.71 (0.81, 3.62)
Total	1625	40.4	1475	34.5	1.25 (1.07, 1.44)

Nonclassifiable plaques are not included in the analyses. Interaction was significant (P=0.005) between age and sex.

sclerotic plaques is lower for women than for men before the age at which the majority of women experience menopause and higher thereafter. Some of the declining prevalence of atherosclerosis with age among older male subjects may be due to a survival selection bias causing an overrepresentation of atherosclerosis-free male survivors.

The overall rate of attendance in our study was high (88%), but lower (≈70%) among the youngest (<35 years old) and oldest (>80 years old) participants. It is likely that this has resulted in a lower prevalence of plaques in the oldest age group, because one must expect subjects with the lowest burden of atherosclerosis-related disease to be overrepresented among the attenders (and survivors). The effect of the lower attendance rate is more unpredictable among younger participants but is probably marginal. The ultrasound examination was conducted without any clinical interview and was blinded with regard to symptoms of atherosclerosis. Some subjects, however, revealed symptoms and fragments of their medical history to the sonographers during the examination. We find it unlikely that this information has influenced our results with regard to plaque prevalence to any significant degree.

No previous large, population-based study has compared the prevalence of carotid plaque in men and women from early adulthood through old age. Prati and colleagues[7] examined a total of 1348 subjects between the ages of 18 and 99 years and did not find plaque before the age of 40 years in either sex. In the MONICA Project Augsburg,[8] a curvilinear relationship between age and carotid atherosclerosis in women seemed to appear but was not discussed by the authors. A direct comparison with our results is difficult, because the analysis in that study was done in 10-year age groups and none of the participants were >65 years old. The Bruneck Ischemic Heart Disease and Stroke Prevention Study,[9] which included 909 subjects >40 years old, also performed analyses on 10-year age groups, and their data on prevalence of atherosclerosis are therefore difficult to compare with our findings. That study showed a declining sex difference in plaque prevalence at high ages similar to those we found. Apart from ultrasound-based studies, information on the prevalence of atherosclerosis and sex differences in the prevalence of atherosclerosis in the general population is scarce. In an autopsy survey, Sternby[21] found age-related prevalence curves for coronary atherosclerosis in men and women similar to those we found for carotid atherosclerosis, with convergence of the prevalence of atherosclerosis in all 3 main coronary arteries in the youngest (<35 years) and oldest (>75 years) age groups.

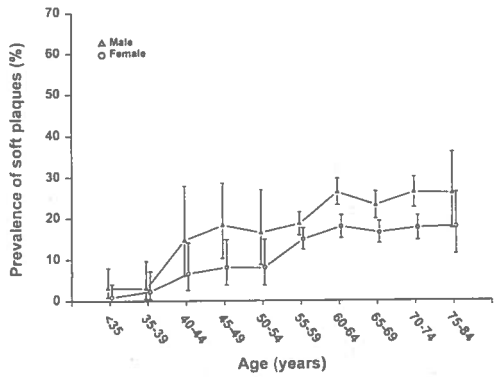

Figure 5. Prevalence of soft carotid plaque by age and sex. The vertical bars denote the 95% confidence intervals of proportions.

It has been discussed whether coronary morbidity and mortality in women is affected by menopause and whether there is an acceleration in the risk of coronary disease and death after menopause. Recently, Tunstall-Pedoe[22] described it as a myth of menopause that risk in women is held low until menopause, when it rebounds, becomes equal, and later surpasses that in men. He showed that the male excess in risk of coronary death continues to rise with age and that the sex gap never closes. Similar findings were reported by Barrett-Connor.[23] Our findings of a premenopausally increasing sex gap in the prevalence of atherosclerosis and a postmenopausal decrease and ultimately closure of the gap at higher ages are not at variance with their findings, because clinical manifestations of vessel wall atherosclerotic lesions may be delayed by many years.

In addition, sex differences in plaque morphology may account for the prevailing male excess risk of coronary death in older age, despite a similar prevalence of atherosclerosis in elderly men and women. Our study shows, to the best of our knowledge for the first time in a general population, that men have softer plaques than women and that the male excess prevalence of soft plaques remains high in old age. One previous clinical study on ultrasound-assessed plaque morphology of stenotic plaques[12] also found that women had harder plaques than men, but that study has limitations

TABLE 4. Prevalence of Ultrasound-Assessed Carotid Atherosclerotic Lesions in Population-Based Studies of Men and Women

Study (n=No. of Participants)	Response Rate, %	Age Range Examined, y	Qualifying Lesion	Age, y	No. of Subjects		Prevalence of Plaque, %	
					Men	Women	Men	Women
Cardiovascular Health Study (CHS), USA (n=5201)[16]	58	≥65	Focal protrusion	65–69	688	1126	67.9	54.2
Atherosclerosis Risk in Communities (ARIC), USA (n=14046)[17]	46–67 (Four centers)	45–64	Two of 3 conditions: (1) Focal protrusion, or (2) High echo-brightness, or (3) IMT≥1.5 mm	60–64	639	463	53.4	41.6
San Diele Project, Italy (n=1348)[18]	75	18–99	Focal protrusion or wall mineralization	60–69	90	104	35.6	29.8
MONICA Project Augsburg, Germany (n=1388)[19]	Not specified	25–65	Focal protrusion	55–64	214	185	49.1	41.1
Bruneck Ischemic Heart Disease and Stroke Prevention Study, Italy (n=909)[20]	94	40–79	Focal protrusion	60–69	119	113	66.4	48.7
Present study, Tromsø, Norway (n=6727)	88	25–84	Focal protrusion	55–64	1422	1453	52.2	40.3
				60–64	686	703	59.5	46.7
				60–69	1308	1453	62.8	51.6
				65–69	622	750	66.6	56.3

IMT denotes intima media thickness. Prevalence of plaque in comparable (overlap or adjacent) age groups is shown. There were small between-study differences in the ultrasound imaging procedures. In the ARIC study, only far-wall lesions were recorded. In the MONICA Project Augsburg, lesions in the external carotid artery were recorded. In the other studies, lesions from the bifurcation and from the common and internal carotid arteries were recorded. In the Tromsø Study, only the right carotid arteries were examined.

because the subjects were selected for carotid endarterectomy. Most myocardial infarctions and sudden coronary deaths are caused by the rupture of soft, lipid-rich plaques.[10,24] If carotid and coronary plaques share common morphological characteristics within individuals, our finding may provide for the continued male excess risk of coronary death in older age. Sex differences in plaque morphology may also partly account for the substantially greater male-to-female ratio for coronary mortality[23,25] than the male-to-female ratio for atherosclerosis throughout life (Figure 3).

Other lines of evidence support our findings that atherosclerosis in women may be qualitatively different from atherosclerosis in men. Coronary bypass surgeons have reported that atherosclerotic tissues in female patients often are more friable and difficult to work with than atherosclerotic tissues in male patients.[26] Furthermore, results from 3 major carotid surgery trials[27–29] showed greater benefit from operations in men than in women. Finally, histological characterization of stenotic plaques studied after carotid endarterectomy,[30] and of plaques in coronary arteries or saphenous vein bypass grafts on autopsy,[31] have shown significant sex differences in plaque morphology.

We conclude that the male-to-female ratio of carotid atherosclerosis increases until the age of 50 years and thereafter declines so that the prevalence of atherosclerosis is similar in elderly men and women. These findings may suggest that events related to menopause may promote atherosclerosis in women. The present study indicates that men have softer plaques than women. We hypothesize that sex differences in plaque morphology may partly account for the prevailing male excess risk of coronary heart disease in the elderly.

Acknowledgments

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PAPER III

Journal of Clinical Epidemiology

ELSEVIER

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Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis
The Tromsø Study

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Abstract

Early menopause has been associated with higher prevalence and incidence of cardiovascular disease and death than late menopause, indicating that early loss of ovarian function and subsequent deficiency of estrogen may promote such diseases. No population-based studies have, however, examined the relation between age at menopause and atherosclerosis. We assessed the prevalence and the extent of carotid atherosclerosis by high-resolution B-mode ultrasound in 2588 postmenopausal women who participated in a population health survey. Information about age at menopause and menarche, parity, use of hormone replacement therapy, and prevalent diseases was collected, and cardiovascular risk factor levels were measured. Women with late menopause and women who ever had used postmenopausal estrogens had significantly less atherosclerosis than women with early menopause and those with never use of estrogen. This study provides further support for the hypothesis that estrogen protects women against cardiovascular disease. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Atherosclerosis; Menopause; Ultrasound; Population-based study

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54–60 yrs
P-values for linear trend

[a]All odds ratios are ag
BMI, body mass index

1. Introduction

Whether menopause alters the risk of coronary heart disease (CHD) remains controversial. The age-related rates of CHD in the general population do not offer strong support for the hypothesis that menopause is associated with a sharp rise in risk of CHD [1,2], and autopsy studies have found no distinct increase in the degree of coronary atherosclerosis with age at menopause [3]. In contrast, recent studies indicate that low age at menopause is associated with increased risk of cardiovascular mortality and morbidity [4,5] and deaths from CHD [6], supporting the hypothesis that loss of ovarian function and subsequent deficiency of estrogen may promote cardiovascular disease. The estrogen hypothesis would be strengthened if there was an association between age at menopause and atherosclerosis. Thus, we have measured carotid atherosclerosis, which is associated with coronary and general atherosclerosis [7–9] non-invasively *in vivo* with ultrasound among 2588 postmenopausal women who participated in a population health survey, and related the prevalence and extent of atherosclerosis to age at natural menopause.

2. Methods

2.1. Subjects and questionnaires

In 1994/1995 a population health survey was conducted in the municipality of Tromsø, Norway, by the University of Tromsø in cooperation with the National Health Screening Service. The study comprised two screening visits 4 to 12 weeks apart. All inhabitants older than 24 years were invited to the first visit, and all subjects aged 55–74 years and random 5–10% samples in the other 5-year age groups were invited to a second visit. The protocol for the first visit was similar to the previous surveys in this population [10], and included standardized measurements of height, weight, blood pressure, and nonfasting serum lipids. Blood pressure and nonfasting serum lipids were remeasured at the second visit, which also included ultrasonographic examination of the right carotid artery. A total of 3323 men and 3404 women, 88% of those eligible, attended both visits and were examined with ultrasound.

The letter of invitation contained questions on previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (all yes/no), treated hypertension (never/previously/currently), and smoking habits. The participants were asked about current smoking (yes/no), previous smoking, and age when they started to smoke. The smoking vari-

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Table 3
Extent of carotid atherosclerosis by age at menopause among postmenopausal women with carotid plaques

	Extent of atherosclerosis (mm)	
	Age-adjusted means	Multivariate adjusted means[a]
Age at menopause		
35–49 yrs (n = 599)	2.94	2.98
49–51 yrs (n = 373)	2.76	2.78
52–53 yrs (n = 172)	2.63[b]	2.63[b]
54–60 yrs (n = 140)	2.62[b]	2.61[b]
P-values for linear trend	0.010	0.004

Extent of atherosclerosis denotes the sum of plaque thicknesses of all plaques present in a single carotid artery (in one to six different locations).
[a]Adjusted for age, use of estrogen, smoking before menopause, body mass index, and length of education.
[b]Significantly different from menopause at 35–49 yrs ($P < 0.05$).

Table 4
Odds ratio for carotid atherosclerosis by use of estrogen

	Odds ratio (95% CI)	
Use of estrogen replacement therapy	Age-adjusted	Adjusted for age, age at menopause, smoking, BMI, and length of education
Never use (reference) (n = 1577)	1	1
Ever use (n = 401)	0.73 (0.57, 0.92)	0.75 (0.59, 0.96)
Unknown use (n = 610)	1.00 (0.82, 1.21)	0.99 (0.82, 1.20)

of this atherosclerosis variable was positively skewed, but log transformation of the values did not change the results notably.

Postmenopausal women who had every used estrogen had significantly lower risk of carotid atherosclerosis than those who reported never use or did not answer the question about use of estrogen replacement therapy (Table 4). Adjustments for age, age at menopause, smoking, body mass index, and length of education, did not change the risk estimate notably. Those with unknown use of estrogen had the same odds ratio for prevalence of plaque as those with never use of estrogen. There was, however, no significant relation between ever use of estrogen and extent of atherosclerosis (data not shown).

In women with plaque, there was no significant association between age at menopause or use of estrogen replacement therapy and softness of plaques (low echogenicity), ORs (95% CI) 1.00 (0.89, 1.13) and 1.27 (0.87, 1.86), respectively.

4. Discussion

The relation between age at menopause and carotid atherosclerosis in a general population has not been investigated previously. In this population-based study we found a significant, inverse relationship between age at menopause and both the prevalence and extent of carotid atherosclerosis. The association was not influenced by potential lifestyle-related confounding factors such as smoking, obesity, length of education, or parity. These findings are in line with results from studies showing an association between early menopause and atherosclerosis-related events such as cardiovascular disease and death [4–6,13–15], although this association was not found in all studies [16]. The risk for coronary heart disease in postmenopausal women seems to be higher than for premenopausal women of similar age, at least when their menopause is caused by oophorectomy [17], and some studies have found that they also have less atherosclerosis [18,19]. A population-based study from the United States (Atherosclerosis Risk in Communities [ARIC] Study) [20] found no association between menopause or hormone replacement therapy and ultrasound assessed carotid artery intima-media thickness. A thick intima-media layer may not, however, always indicate the presence of atherosclerosis. Thus, the mean intima-media thickness in the carotid artery of the postmenopausal women in the ARIC study was only 0.67 mm, compared to the mean value of the maximum plaque thickness of 2.01 mm in our study. Autopsy studies have shown an association between the time interval from oophorectomy to expected menopause and coronary atherosclerosis [21], supporting our findings of a relationship between early menopause and carotid atherosclerosis, although hormonal alterations caused by complete resection of normally functioning ovaries are not fully comparable with the gradual cessation of ovarian function leading to a natural menopause.

In a recently published prospective study, Hu *et al.* [5] found that low age at menopause was significantly related to cardiovascular disease for all women and for those who had ever smoked, but not for never-smokers. We found a significant age-adjusted inverse relationship between age at menopause and atherosclerosis (P-value for linear trend, 0.04) also for the 46% of the women who never had smoked before menopause.

The early menopause age group in our study comprises a large age-span (35–48 years). Comparisons of subgroups within this group showed no significant association between very low age at menopause and atherosclerosis. This may partly be caused by misclassification, because recall bias may increase with increasing time since menopause. Another explanation may be that the negative effect of a very early menopause may be diluted by long-time effects of other risk factors for atherosclerosis. Bias due to premature, surgical menopause may also be an explanation. The effect of hysterectomy and bilateral oophorectomy on development of atherosclerosis is expected to act oppositely, hysterectomy leaving, at least for the first postoperative years, an approximately normal ovarian function, whereas oophorectomy will cause an abrupt and total cessation of estrogen production in the ovaries compared to a normal menopause. Such a differential effect of surgical menopause on cardio-

vascular disease has previously been reported [17]. A limitation with our study is that we had no information from the questionnaire on whether the menopause was natural or secondary to surgery. We therefore scrutinized the medical records of the 90 women who reported an age at menopause of 35–39 years. Hysterectomy was found to be the cause of menopause in 31 women (34%) and bilateral oophorectomy (combined with hysterectomy in all cases) in five women (6%). When these 36 women were excluded from the analysis the relative risk (odds ratio) for atherosclerosis was not changed. When the menopause age group of 35–48 years was split in two groups of 35–39 years and 40–48 years, the result from excluding the 36 women with previous hysterectomy or oophorectomy was a nonsignificant increase of risk for atherosclerosis of the lowest menopause age group compared to the other four menopause age groups.

The risk for carotid atherosclerosis declined with age at menopause, but those with a very late menopause (i.e., above 54 years), however, had no further decrease in the prevalence of atherosclerosis. Instead, this group had a nonsignificant increase in atherosclerosis prevalence. A reversed J-shaped relationship between age at menopause and prevalence for cardiovascular disease has also been found [15]. The reason for this deviation from linearity between age at menopause and atherosclerosis is difficult to explain by known biological mechanisms.

The relation between age at menopause and atherosclerosis remained significant when the analysis was restricted to women who denied ever using postmenopausal estrogen. This implies that misclassification of age at menopause due to continued bleedings among estrogen users can not explain our findings.

The association between menopause and cardiovascular disease has been attributed to estrogen deficiency, and the increased cardiovascular risk of an early menopause related to the longer duration of this deficiency. Observational studies have found that use of postmenopausal hormone replacement therapy is associated with approximately 50% lower risk for coronary heart disease compared to untreated women [16]. It has been claimed that the observed positive effect of estrogen in observational studies is due to selection biases. Thus, the only randomized clinical trial on the effect of female hormones on coronary heart disease and death in postmenopausal women with coronary disease did not find any effect after 4.1 years of follow-up [22].

We found that postmenopausal women who had ever taken estrogen had approximately 30% lower risk for atherosclerosis as compared with never-users. If previous use of contraceptive pill (14% of the women) was entered into the analysis as a covariate no change of risk estimates occurred. Unfortunately, we had no information about the length of estrogen therapy. However, as 85% of the women never had used hormone replacement therapy, information about the length of estrogen probably would have contributed little. Our findings correspond to results from case–control studies of coronary atherosclerosis and use of estrogen in postmenopausal women [23,24]. These studies have been performed among women with coronary disease, and are therefore not fully comparable with our population-based approach. Interestingly, our data suggest that the decrease in risk for atherosclerosis associated with late menopause may be of similar size as the decrease in risk associated with postmenopausal therapy (i.e., the risk for atherosclerosis lowered by approximately 30%), although one should be cautious drawing conclusions from cross-sectional data. The women who had ever used estrogen had significantly lower levels of systolic blood pressure and total cholesterol, but not higher HDL-cholesterol than the other women in the study. When also controlling for these variables the association between ever use of estrogen and prevalence atherosclerosis was slightly attenuated [OR (95% CI), 0.79 (0.62, 1.01), P = 0.06]. However, since the serum lipid levels may change during estrogen therapy [25], adjusting for cholesterol may not be appropriate.

In summary, the present study provides further support for the hypothesis that estrogen protects women against cardiovascular disease by showing that both late menopause and use of postmenopausal estrogen replacement therapy is associated with a moderately reduced risk of atherosclerosis.

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PAPER IV

Prediction of Mortality by Ultrasound Screening of a General Population for Carotid Stenosis. The Tromsø Study

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Abstract

Background and Purpose: The extensive use of ultrasound examinations of carotid arteries has revealed stenosis in many asymptomatic subjects, and clinical studies have shown that carotid stenosis is a risk factor for cardiovascular disease and death. However, there is scarce information about stenosis as detected in a general population and the relation with mortality. The purpose of this population-based study was to assess whether carotid stenosis is a predictor of death.

Methods: In 1994/1995, 248 subjects with suspect carotid stenosis were identified among 6727 men and women aged 25-84 years examined with ultrasound. These subjects and 496 age-and-sex matched controls were followed for 4.2 years, and number and causes of deaths were registered.

Results: The unadjusted relative risk (95% CI) for death was 2.72 (1.57-4.75) for subjects with stenosis compared with controls. Adjusting for cardiovascular risk factors increased the relative risk to 3.47 (1.47-8.19). The adjusted relative risk in persons with stenosis and no cardiovascular disease or diabetes was 5.66 (1.53-20.90), which was higher than in subjects with stenosis and selfreported disease (1.79 (0.75-4.27)). There was a dose-response relationship between degree of stenosis and risk of death (p=0.002 for linear trend). Carotid stenosis was a stronger predictor of death than selfreported cardiovascular disease or diabetes.

Conclusions: Carotid stenosis is a strong and an independent predictor of death.

The use of ultrasound examinations of carotid arteries in clinical practice, clinical trials, and population health surveys, has identified many persons with asymptomatic carotid stenosis. In some studies where patients are referred to ultrasound examinations on various clinical indications, carotid stenosis has shown to be a significant predictor of death.[1-3] Randomized clinical trials designed for comparison of surgery or medical treatment as the most appropriate treatment for carotid stenosis, have found that both symptomatic[4, 5] and asymptomatic subjects[6] with stenosis are at high risk of cerebral stroke and cardiovascular death.

In contrast, only two population-based studies[7, 8] have examined the relationship between carotid stenosis and mortality. Both these studies included elderly (≥65 years) subjects only, and one included men only.[8] The purpose of this population-based study of 6727 male and female subjects in the age range of 25 to 84 years, revealing 248 cases with suspected carotid stenosis, was to assess whether carotid stenosis, as detected by ultrasound examination of a general population, is a predictor of death.

Methods

Population

In 1994/1995, a population health survey was conducted in the municipality of Tromsø, Norway, by the University of Tromsø in cooperation with the National Health Screening Service. The study comprised two screening visits 4 to 12 weeks apart. All inhabitants in the municipality older than 24 years were invited to the first visit, and all subjects aged 55-74 years and 5 % random samples in the other 5-year agegroups were invited to both visits. In addition, 307 men aged 45-54 years were invited because they had participated in an intervention study in a previous survey of the Tromsø Study, why the sample size for these agegroups was higher than 5 %. The protocol for the first visit was similar to the previous surveys in this population,[9] and included standardized measurements of height, weight, blood pressure, nonfasting serum lipids, and fibrinogen. Blood pressure and non-fasting serum lipids were remeasured at the second visit, which also included ultrasonographic examination of the right carotid artery. A total of 3323 men and 3404 women, 79 % of those eligible, attended both visits and were examined with ultrasound. The letter of invitation contained questions on previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (yes/no), treated hypertension (never/previously/currently), and cigarette smoking. The questionnaire was checked for logical

inconsistencies at the examination. The study was approved by the Regional Committee for Medical Research Ethics and written consent was obtained from all participants.

Cardiovascular risk factors

Height and weight were measured in light clothing without shoes; body mass index (BMI) was calculated as weight in kilogram divided by the square of the height in meter. Blood pressure was recorded in a separate, quiet room by a specially trained nurse. An automatic device (Dinamap Vital Signs Monitor, Tampa, Fla) was used. Serum cholesterol and triglycerides were analyzed by standard enzymatic methods and fibrinogen was measured using the PT-Fibrinogen reagent (Instrumentation Laboratory, Italy). The serum analyses were performed at the Department of Clinical Chemistry, Tromsø University Hospital.

Ultrasonography

The ultrasound methods have been described in detail previously.[10] Briefly, high-resolution B-mode ultrasonography was performed with an ultrasound scanner (Acuson Xp10 128, ART-upgraded) equipped with a linear array transducer. The common, internal, and external carotid arteries were identified by combining B-mode (7 MHz) and Color-Doppler/pulsed-wave Doppler (5 MHz) ultrasound. We attempted to identify and record atherosclerotic plaques from 6 sites of the carotid artery: the near and far walls of the internal carotid artery (ICA), the bifurcation segment of the common carotid artery (CCA), ie, the distal part of the CCA, and the CCA from the bifurcation and downstream to the supraclavicular region. A random sample of 784 subjects were examined on both right and left carotid arteries to provide information about bilateral carotid stenosis. A carotid artery was defined as being stenotic if one or both of the two criteria below were met: 1) Hemodynamic criterion: Peak systolic velocity at the tightest, stenotic part (PSVs) ≥ 0.2 m/sec higher than peak systolic velocity at the point of reference (PSVr), or ≥ 0.1m/sec if the stenosis was located at the carotid bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery was used as the point of reference. 2) Structural criterion: Plaque causing 35% or more reduction in lumen diameter on a longitudinal B-mode scan. The degree of stenosis was calculated by the peak systolic velocity ratio method: (1–PSVr/PSVs) x 100%. Complete occlusion of the carotid artery was graded as 100% stenosis.

Three sonographers screened the subjects; one was a neurologist (OJ) with ten years experience in ultrasound examination of the carotid artery, the second was a physician (ES-B), and the third a specially trained technician. A two months training protocol was completed before the survey started. A reproducibility study on

plaque occurrence found that between- and within-sonographer agreement was substantial with κ-values (95% CI) of 0.72 (0.60 to 0.84) and 0.76 (0.63 to 0.89), respectively.[10]

Cases with carotid stenosis and control subjects

For each case with suspected stenosis two controls were randomly drawn among subjects who did not have stenosis. The cases and controls were matched by age (±2 years), sex, date of examination, and living area within the municipality (rural or urban areas).

All persons with suspected stenosis and one of the two controls in each triplette were referred to the outpatient clinic at Department of Neurology, University Hospital, Tromsø, for clinical examination and ultrasonographic reevaluation and reclassification. All examinations were performed by two experienced neurologists (OJ, EBM). A flowchart of the selection procedures is shown in Figure 1.

The subjects were followed from the date at screening or at ultrasound reclassification to December 1st, 1998, or to the date of death. Deceased subjects were identified by linkage to the National Population Register, and details of all deaths were documented whenever possible by hospital records and autopsy reports.

The reproducibility on the grading of stenosis at reclassification was satisfactory with a mean absolute difference between sonographers of 10.8%.[11] The κ-values (95% CI) for agreement on categories of stenosis dichotomized at various cutoff points (50%, 60%, and 70% stenosis) were 0.57 (0.33-0.81), 0.66 (0.4-0.91), and 0.79 (0.54-1.00), respectively.[11]

Statistical analysis

Differences between cases and controls in mean values of baseline cardiovascular risk factors were tested for statistical significance by using two-way analysis of variance with match-number of triplettes (1-248) and stenosis (yes/no) as factors. Differences in proportions were tested by χ^2-tests and Fisher's exact test (2-tail). Kaplan-Meier method was used to calculate survival for the groups, and the logrank test was used to test the difference in survival between the groups. Death rates were calculated as the number of deaths by person-years of observation (time to death or censoring). Unadjusted relative risks were estimated by calculation of ratios of mortality rates. Cox proportional hazards regression model was used to estimate the influence of carotid stenosis on death adjusted for risk factors. Stratified analyses were used in analysing the matched triplettes (1 case and 2 controls) adjusted for smoking, body mass index, systolic blood pressure, total and HDL cholesterol, triglycerides, and fibrinogen.

To test whether there was a dose-response relationship between degree of carotid stenosis and mortality the subjects were categorized in five groups according to degree of stenosis based on findings at the ultrasound reclassification at the outpatient clinic: 1) Subjects without carotid stenosis (reference group), 2) those with a less than 45% stenosis, 3) those with stenosis between 45% – 74%, 4) those with stenosis between 75% – 99%, and 5) those with 100% stenosis (ie, occlusion), respectively. The strength of dose-response relationship was expressed by p-values for linear trend in the Cox regression model. When bilateral stenoses were present the measures from the tightest stenosis of the two sides were used in the calculation of degree of stenosis.

Two-sided values of $p<0.05$ were considered statistically significant. The SAS software package version 6.12 was used.[12]

Results

A total of 248 subjects with suspected carotid stenosis at the screening and 496 matched controls were included in the analysis of screening results (Analysis A, Figure 1). There was a male predominance (61.3%) (Table 1). Cases had higher levels of systolic blood pressure, total cholesterol, triglycerides, and were more likely to smoke, being treated for hypertension, and having a history of cardiovascular disease. There was no significant difference between cases and controls with regard to BMI, HDL-cholesterol, diastolic blood pressure, and the prevalence of diabetes mellitus.

The follow-up time until death or the censoring date of December 1, 1998, lasted up to 4.2 years. The mean (median) observation time was 3.6 years (3.8 years) for the cases, and 3.8 years (3.8 years) for the controls. Table 2 shows that among the 248 cases, 30 persons (12.1%) died during the observation time compared with 23 deaths (4.6%) among the 496 controls. In cases, the death rate was 3.35 per 100 person-years compared with 1.23 per 100 person-years in controls, giving a relative risk (95% CI) of 2.72 (1.57-4.75). After adjustment for baseline cardiovascular risk factors, the relative risk increased to 3.47 (1.47-8.19). The relative risk of death for cases with stenosis was greater in persons without CVD or diabetes (3.08) than in persons who reported CVD or diabetes (1.79) (Table 2). After multivariate adjustment, the relative risk for death associated with stenosis became higher, especially among persons without CVD or diabetes (5.66). Table 2 also shows that the death rate was similar in cases with stenosis who did not have CVD or diabetes (3.14 deaths per 100 pyar) and in cases with stenosis who also had CVD or diabetes (3.61 deaths per 100 pyar). The logrank test showed significant statistical difference between the survival curves for those with and without carotid stenosis (p=0.0002) (Figure 2). The difference was significant both in men (p=0.007) and in women (p=005).

Cardiovascular disease was the main cause of death in both controls and cases (Table 3). However, death due to cardiovascular disease was more common among subjects with stenosis than in controls. The absolute risk of death from ischemic cerebral stroke was small, even among subjects with stenosis.

Table 4 shows mortality for the subjects who were reexamined at the outpatient clinic (n=477) and reclassified with regard to presence of stenosis and categorized according to degree of stenosis (Analysis B, Figure 1). The death rates and unadjusted and adjusted relative risks for death increased by increasing degree of stenosis (Table 4). Thus, unadjusted and adjusted relative risks (95% CI) for death increased to 7.47 (2.53-20.49) and 5.50 (1.63-18.52) among those with occlusion (p=0.002 for linear trend), indicating a significant dose-response of carotid atherosclerosis on mortality. Among the 237 subjects who had stenosis, the adjusted relative risk (95% CI) for death per 10 % increment of degree of stenosis was 1.20 (1.03-1.41) (data not displayed). Death was significantly (p=0.04) associated with CVD or diabetes regardless of status of stenosis. No additional information was achieved when the analyses were stratified by gender.

Discussion

This study shows that carotid stenosis is a strong and independent predictor of death. Cases with stenosis who reported CVD or diabetes had only slightly higher death rate than those with stenosis who did not report CVD or diabetes, which means that prevalent CVD or diabetes did not add much to the risk of death in subjects with carotid stenosis. The higher relative risk associated with stenosis in subjects without clinical disease (RR=3.08) compared to cases with stenosis who reported prevalent CVD or diabetes (RR=1.79) is due to low death rate among stenosis-free controls without clinical disease. The multivariate adjusted relative risk for death associated with stenosis is particularly strong for subjects who reported no prevalent CVD or diabetes (RR=5.66). At the screening, 214 subjects reported CVD or diabetes (22 deaths) and 530 subjects reported no such diseases (31 deaths).

There was a dose-response relationship between degree of stenosis and risk of death. The highest relative risk appeared among the 19 persons who had carotid occlusion (six of them had no CVD or diabetes) with a death rate of 9.7 per 100 pyars. This implies that as many as 30 % of these subjects died during follow-up, compared with 4.5% of subjects without stenosis. Advanced carotid atherosclerosis therefore seems to be a strong predictor of death, also in the absence of clinical disease. Only 55 % of the 60 cases with a stenosis more than 70% reported coronary disease, previous stroke, or diabetes mellitus. The death rate for the 33 cases with

clinical disease and with stenosis over 70% was 8.1 per 100 person-years compared with 7.8 per 100 person-years in the 27 subjects without such diseases (data not displayed).

Cardiovascular disease was the cause of death in 80 % of cases with stenosis compared to 43.5 % in those without stenosis. In the group of stenosis, 6.7% died from an ipsilateral ischemic stroke. The majority died from coronary heart disease. Several other studies have also found that carotid stenosis is a stronger predictor of cardiac death than death from cerebral stroke.[1-3, 13] This is also in line with ultrasound and autopsy studies showing that the presence and extent of carotid atherosclerosis correlate well with atherosclerosis elsewhere in the circulation including the coronary arteries.[14-16]

Subjects with carotid stenosis were offered annual clinical and ultrasound follow-up, whereas the control subjects were examined only at the entry of the study. Those cases who disclosed early symptoms or signs consistent with heart or cerebrovascular disease were given medical advice or therapy, or were referred for further investigations and treatment. This may have resulted in a lower mortality rate among cases, and thus causing an underrating of the relative risk for death in those with stenosis compared to stenosis-free controls.

To our knowledge, only two studies have previously evaluated whether carotid stenosis, as detected by ultrasound screening of a general population, is a predictor of death. In the Cardiovascular Health Study (CHS),[7] 5114 men and women ≥65 years old were examined by ultrasound and classified according to degree of stenosis. Unadjusted relative risk for death among subjects with stenosis compared to those without stenosis (ie, those without carotid atherosclerotic plaques) were slightly higher, and adjusted relative risk were lower compared to our findings. The mean age in our study was 6 years lower than in CHS, and the participation rate was higher in our study, 88% versus 57% in CHS. The higher age in CHS may have contributed to the lower adjusted relative risk estimates compared to the results of our study. Similarly to our findings, they found the highest death rates among subjects with carotid occlusion, and that carotid stenosis was a better predictor of death than selfreported cardiovascular disease.

In a smaller Swedish study on 10-years mortality among 68 years old men,[17] the annual death rate among subjects with carotid stenosis (n=117) was higher than in those without stenosis (relative risk=1.45, p=0.03). However, the association disappeared when adjusting for other risk factors. In a later publication,[8] they found that this higher relative risk for death was present only among those men who did not suffer from ischemic heart disease at baseline. The lower relative risk for death in that study compared to our results may be due to higher cardiovascular morbidity (eg, 42.3% had prevalent ischemic heart disease compared to 24.0% of those who reported coronary disease in our population older than 67 years) and male sex.

Association between carotid stenosis and death has been found in clinical studies.[1, 3] However, different inclusion criteria in population-based and clinical studies make comparisons difficult. In general, patients referred to ultrasound laboratories on clinical indications supposedly have more active clinical disease and consequently higher risk of death.

In a population-based study from Framingham,[13] the presence of neck bruit, a clinical finding being highly correlated with carotid stenosis, was associated with a 1.7-fold higher relative risk of death in men ($P<0.05$), and a 1.9-fold in women ($P<0.01$); and Wiebers et al[2] in another population-based study, found the relative risk of death by neck bruit to be 2.2.

Prompted by recently reported beneficial effect of endarterectomy in patients with asymptomatic carotid stenosis,[6] the value of screening for asymptomatic carotid stenosis has been discussed. It has been found that ultrasound screening for carotid stenosis is not cost-effective regarding carotid endarterectomy.[18, 19] Any benefit from regular screening, however, is not only restricted to a possible impact on stroke incidence caused by carotid endarterectomy. Most of people with carotid stenosis die from coronary heart disease and not from stroke,[1-3, 7, 13, 17] as also shown in the present study. The main consequence of ultrasound screening of a general population is that subjects with high risk for coronary disease will be identified. Medical intervention as part of preventive strategies may therefore save as many from disease and death as carotid endarterectomy. Our results are not an argument for routinely screening of general populations to detect carotid stenosis. That is hardly a cost-effective procedure.The main purpose of our study was to use ultrasonographic measurements as part of the study of cardiovascular disease etiology. However, a lot of subjects will incidentally have asymptomatic carotid stenosis disclosed by ultrasound examinations performed as part of scientific studies or on clinical indications. We therefore believe that it must be of interest to know the risk of death in such subjects.

This study has shown that the presence of carotid stenosis as detected by ultrasound screening of a general population is a strong predictor of death and stronger than self-reported cardiovascular disease or diabetes. The relative risk for death is particularly strong for subjects with stenosis who reported no prevalent CVD or diabetes. There is a dose-reponse relationship between degree of carotid stenosis and death. Subjects with carotid stenosis should be treated as high-risk subjects and offered clinical follow-up to lower cardiovascular risk factor levels and to recognize early clinical signs of cardiovascular disease for further diagnostic and therapeutic interventions.

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Table 1. Screening characteristics of participants with suspected carotid stenosis and matched controls.

	Cases	Controls	p-value for group difference
No. of subjects	248	496	
Male, %	61.3	61.3	matching variable
Age, y	67.6 (6.3)	67.4 (6.2)	matching variable
Current smoking, %	39.5	22.8	<0.001
Body mass index, kg/m^2	26.3 (4.2)	26.2 (3.8)	0.8
Systolic blood pressure, mm Hg	149.8 (22.5)	143.7 (20.5)	0.0002
Diastolic blood pressure, mm Hg	81.2 (12.4)	81.1 (10.9)	0.9
Serum total cholesterol, mmol/L	7.09 (1.32)	6.74 (1.21)	0.0002
Serum HDL-cholesterol, mmol/L	1.42 (0.42)	1.48 (0.44)	0.052
Serum triglycerides, mmol/L	1.93 (1.05)	1.71 (0.96)	0.004
Fibrinogen, g/L	3.83 (0.95)	3.53 (0.88)	0.0001
Treated hypertension, %	42.9	22.6	<0.001
CVD or diabetes, %	44.0	21.2	<0.001
Myocardial infarction, %	16.7	7.7	<0.001
Angina pectoris, %	27.2	11.3	<0.001
Cerebral stroke, %	9.3	3.3	<0.001
Diabetes, %	5.7	4.9	0.6

Values are means (SD) and percentages.

CVD (cardiovascular disease) indicates self-reported myocardial infarction, angina pectoris, or cerebral stroke.

Table 2. Death rates and relative risk of death in cases and age-and-sex matched controls based on screening results.

	All subjects		Persons without CVD and diabetes		Persons with CVD or diabetes	
	Cases	Controls	Cases	Controls	Cases	Control
No. of subjects	248	496	139	391	109	105
No. of deaths	30	23	16	15	14	8
Person-years of follow-up (pyar)	897	1868	510	1471	388	397
Death rate per 100 pyar	3.35	1.23	3.14	1.02	3.61	2.02
Relative risk (95% CI) of death	2.72 (1.57-4.75)		3.08 (1.49-6.36)		1.79 (0.75-4.27)	
Adjusted* relative risk (95% CI)	3.47 (1.47-8.19)		5.66 (1.53-20.90)†		1.95 (0.76-5.02)†	

CVD denotes selfreported myocardial infarction, angina pectoris, or cerebral stroke.

*Adjusted for smoking, body mass index, systolic blood pressure, total and HDL cholesterol, triglycerides, fibrinogen, myocardial infarction, stroke, angina pectoris, and diabetes in a proportional hazard regression model (Cox) stratified by age-and-sex matched triplettes (one case and two controls).

† The matched design is broken, and age and sex are also adjusted for.

Table 3. Cause specific death among cases with suspected stenosis and controls based on screening results.

Causes of death	Number of deaths (%)	
	Cases (n=248)	Controls (n=496)
Cardiovascular disease*	24 (9.7)	10 (2.0)
Ischemic stroke	4 (1.6)†	2 (0.4)
Malignant disease	2 (0.8)	8 (1.6)
Other causes‡	4 (1.6)	5 (1.0)
All	30 (12.1)	23 (4.6)

*Cardiovascular disease includes myocardial infarction, congestive heart failure, cerebral stroke (ischemic stroke or cerebral hemorrhage), or ruptured abdominal aorta aneurysms.

†Two subjects got ischemic stroke ipsilateral to stenosis, the two other had a brainstem infarction and a cerebral hemorrhage, respectively.

‡Other causes include infections, chronic obstructive lung disease, trauma, or gastrointestinal disease.

Table 4. Death rates and relative risk of death for subjects by degree of stenosis as verified at the ultrasound reexamination.

	Degree of stenosis					P-value for linear trend
	Absent	<45%	45% - 74%	75% - 99%	Occlusion	
No. of subjects	240	109	73	36	19	
No. of deaths	10	8	8	7	6	
Person-years of follow-up (pyar)	770	379	241	121	62	
Death rate per 100 pyar	1.30	2.11	3.32	5.80	9.68	
Rel. risk of death (95% CI)	1	1.62 (0.63-4.12)	2.55 (0.98-6.49)	4.46 (1.62-11.69)	7.47 (2.53-20.49)	
Adjusted rel. risk of death (95% CI)*	1	1.32 (0.48-3.62)	2.22 (0.81-6.12)	3.24 (1.12-9.35)	5.50 (1.63-18.52)	0.002

*Adjusted for age, sex, CVD or diabetes, smoking, body mass index, systolic blood pressure, total and HDL cholesterol, triglycerides, and fibrinogen.

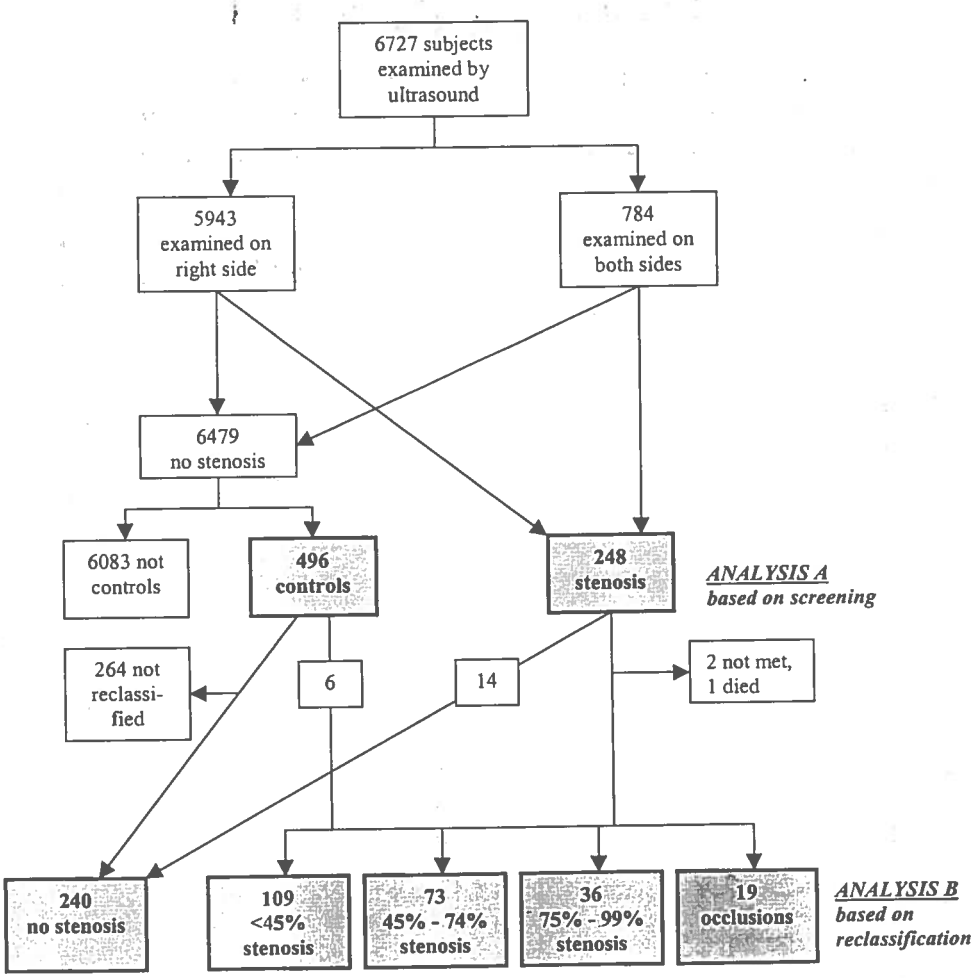
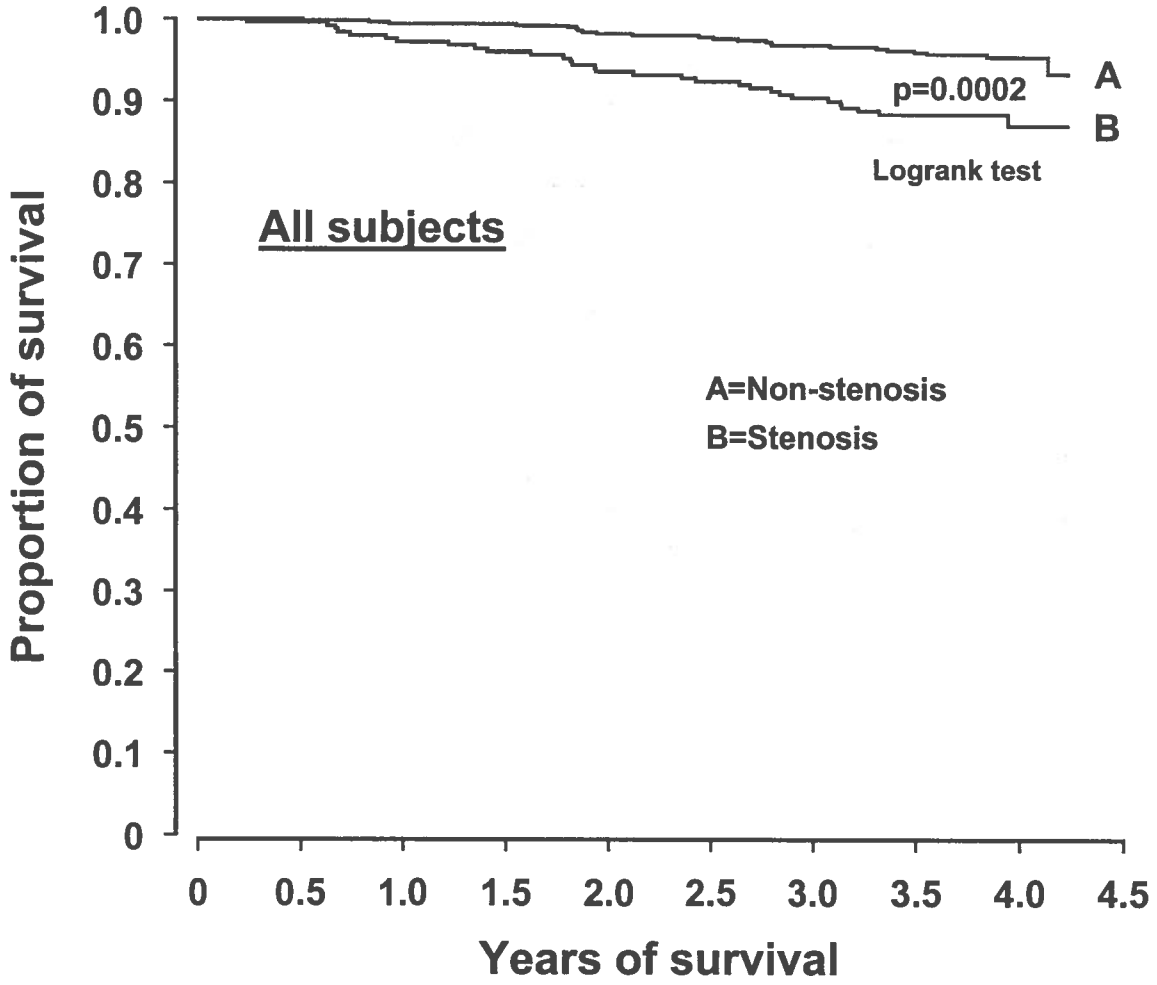


Figure 1. Flowchart of cases with carotid stenosis and control subjects.

Figure 2


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Proportion of survival
p=0.0002
A
B
Logrank test
All subjects
A=Non-stenosis
B=Stenosis
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
Years of survival

APPENDIX A

Adjustments of the ultrasound instrument

APPENDIX A

INSTRUMENT ADJUSTMENT

Due to the higher loss of sonic energy with high frequencies than with low frequencies, ultrasonic waves of lower frequencies (e.g., 5 MHz) better are used, instead of the usual high frequency ultrasound waves of 7 MHz, if the target for insonation is deeply located carotid arteries, as in obese subjects. The instrument setting therefore has to provide a compromise between high enough frequencies transmitted to reveal small objects, but not too high so information is unable to obtain from obese subjects or from deeply located vessels. Changing the frequency should, however, be done only as an exception (standardization should best be maintained).

Other instrument adjustment procedures may also have impact on the information gained from ultrasound images and from Doppler/colour Doppler signals. Transmit power setting determines how much acoustic power the transducer delivers into the body. When transmit power is lowered, the ultrasound instrument automatically increases the receiver gain (increases the amplitudes of in-coming ultrasound), and the B-mode images will not appear much different from images of the original transmitted power. The gain should generally not be set so high that anatomical structures that normally reflect no or weak ultrasound signals are visible on B-mode images, for example flowing blood (or when artifact colour Doppler signals are seen outside the vessel lumen). Conversely, the gain should continuously be adjusted to ensure that structures in the ultrasound field are not concealed due to too little transmission of power.

The log compression function controls the grey scale display of the image. This does not change the number of grey shades displayed, which in our instrument always is 256. However, when log compression is increased, the echogenicity (brightness) of a specific amplitude signal also will increase. (The amplitude of an ultrasonic wave corresponds to the energy (power), not the frequency, of ultrasound). The use of log compression adjustments influences the contrast resolution (the ability to distinguish two different echogenicities, that are similar but not identical, as two separate and differing echogenicities. An example of the relevance of good contrast resolution is the ability to distinguish a soft thrombus from adjacent structures such as the vessel wall or flowing blood.

Preprocession acts as an edge enhancement function. The process of edge enhancement allows adjustment of received echo information to vary the transition zones between areas of differing echogenicity. To adjust preprocession means to change the impression of "smoothness" of structures within the B-mode image. Low preprocession gives images with sharp and crisp borders, the structures appear a little grainy and it looks like a "overload" of details in the image. High preprocession makes structures in images looking smooth, structures look confluent and the edges less descernible.

The adjustment of postprocession also changes the appearance of B-mode (and colour Doppler) images but does not add new information to the image. The method of postprocession enables the ultrasound instrument to differentially enhance amplitudes of incoming ultrasonic waves. High amplitudes, i.e., "strong" signals may be attenuated and "weak" signals enhanced, or vice versa. The images consequently will differ in smoothness and grey scale contrasts.

Persistence is some sort of averaging images so that "history" from previous images adds to the currently displayed B-mode or colour Doppler image. By adding information from previous frames, it is easier to distinguish very subtle echogenic changes within the image, and the colour Doppler signals appear more fluent and continuous giving a more convincing impression that blood is flowing.

Adjustment of transmit zones allow the transmitted ultrasound beams to highlight the area of interest in the image, both B-mode and Doppler presentations. It is useful to enhance the resolution of small anatomical structures.

Another way to enhance spatial resolution and to facilitate visualising and measurement of target objects in the ultrasound field is by utilizing the so-called Regional Expansion Selection option (RES). The sonographer may select the region of interest where objects partly undergo a simple magnification and partly become more easily revealed because the spatial resolution is increased due to increase of ultrasound scan line density.

APPENDIX B

Questionnaire 1, Tromsø Study IV, 1994/1995

(In norwegian and english language versions)

Innbydelse til

HELSEUNDERSØKELSEN

Fødselsdato Personnr. Kommune Kretsnr.

Velkommen til helseundersøkelsen i Tromsø!

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

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

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

Vennlig hilsen

Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

EGEN HELSE

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

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

Har du, eller har du hatt:

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

Bruker du medisin mot høyt blodtrykk?

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

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

Har du de siste to ukene følt deg:

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

RØYKING

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

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

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

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

Røyker du selv:

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

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

Hvis du røyker daglig nå eller har røykt tidligere:

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

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

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

MOSJON

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

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

KAFFE

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

Kokekaffe	58	Antall kopper ____
Annen kaffe	60	Antall kopper ____

ALKOHOL

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

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

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65 Øl glass ____ Vin glass ____ Brennevin 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
Bløt (soft) margarin		☐ 4
Smør/margarin blanding		☐ 5
Lettmargarin		☐ 6

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

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

Hva slags arbeidssituasjon har du nå?

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

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

Mottar du nå noen av følgende ytelser?

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

SYKDOM I FAMILIEN

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

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

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

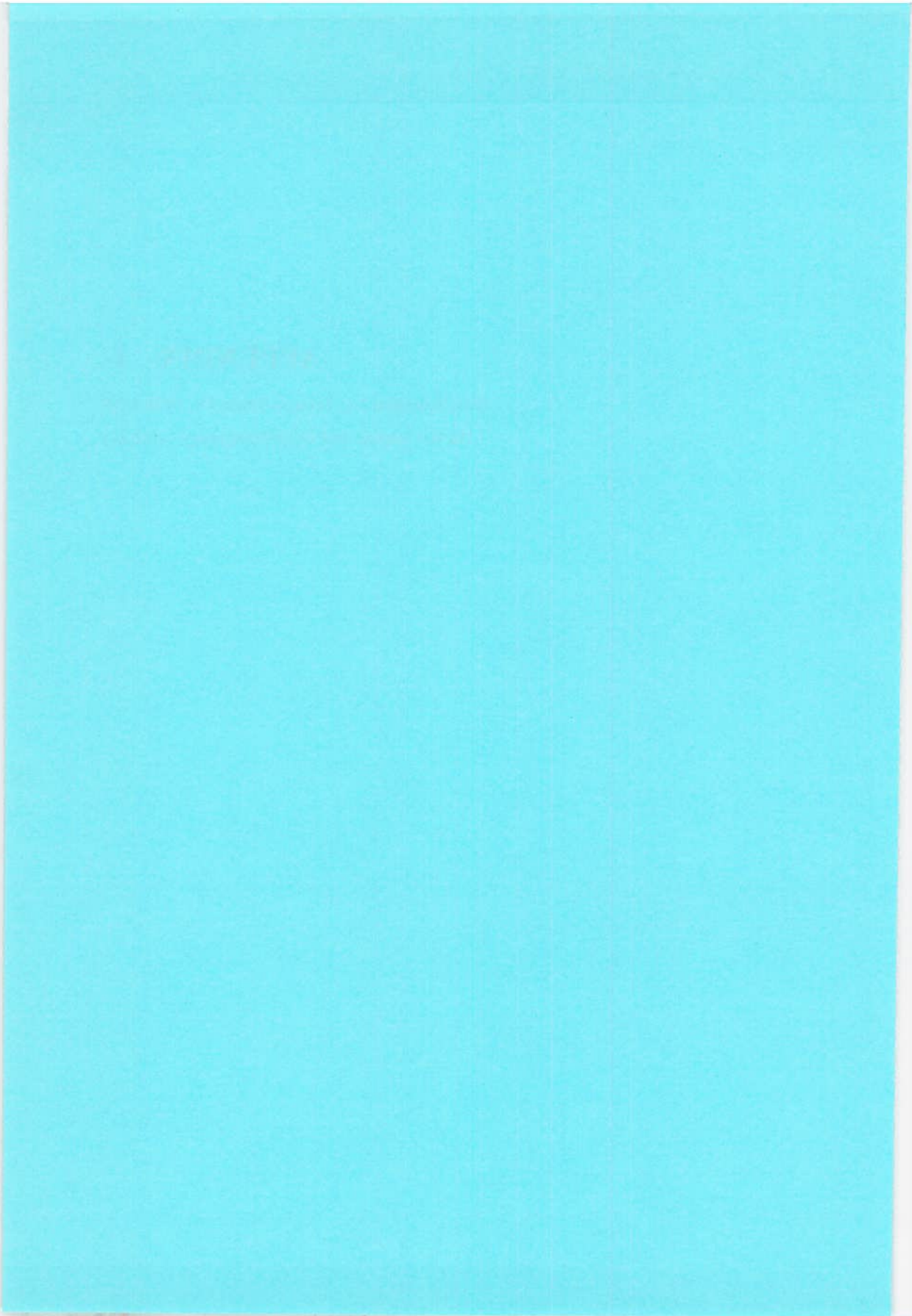
Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)?

YES	NO	DON'T KNOW
☐	☐	☐

APPENDIX C

Questionnaire 2A, Tromsø Study IV, 1994/1995

(In norwegian and english language 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. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ☐ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ☐ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

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

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

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

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

EGNE SYKDOMMER

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

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

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

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

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

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

SYKDOM I FAMILIEN

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

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

SYMPTOMER

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

Hvor ofte er du plaget av søvnløshet?

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

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

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

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

Hvor ofte er du plaget av hodepine?

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

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

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

BRUK AV HELSEVESENET

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

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

LEGEMIDLER OG KOSTTILSKUDD

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

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

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

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

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

VENNER

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

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

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

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

KOSTVANER

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

Den rekker til omtrent 265 ____ skiver

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

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

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

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

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

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

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

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	☐	☐	☐ 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?	Ja	Nei
330	☐	☐

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?	Ja	Nei
339	☐	☐

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?	Ja	Nei
343	☐	☐

Hvis "Ja", i hvilket svangerskap?	Svangerskap Første	Senere
For høyt blodtrykk 344	☐	☐
Eggehvite i urinen 346	☐	☐

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

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

PREVENSJON OG ØSTROGEN

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

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå? 376

Hvis du bruker eller har brukt p-pille:

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

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

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

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? 386 _____ år

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

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

APPENDIX D

Questionnaire 2B, Tromsø Study IV, 1994/1995

(In norwegian and english language versions)

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

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

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

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

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

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø

Statens helseundersøkelser

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

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

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

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24-28

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

Hvordan var de økonomiske forhold i familien under din oppvekst?

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

Hvor gamle ble dine foreldre?

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

BOLIG

Hvem bor du sammen med?

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

Hvilken type bolig bor du i?

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

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

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

TIDLIGERE ARBEID OG ØKONOMI

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

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

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

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

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

Hva slags pensjon har du?

- Minstepensjon ..... 59 ☐
- Tilleggspensjon ..... 60 ☐

Hvordan er din økonomi nå?

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

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?
- Ja, dårligere 62 ☐ 1
- Nei, uforandret ☐ 2
- Ja, bedre ☐ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?
- Mye dårligere 63 ☐ 1
- Litt dårligere ☐ 2
- Omtrent lik ☐ 3
- Litt bedre ☐ 4
- Mye bedre ☐ 5

EGNE SYKDOMMER

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

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

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

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

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

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

SYKDOM I FAMILIEN

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

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

SYMPTOMER

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

Hvor ofte er du plaget av søvnløshet?
- Aldri, eller noen få ganger i året 196 ☐ 1
- 1-2 ganger i måneden ☐ 2
- Omtrent en gang i uken ☐ 3
- Mer enn en gang i uken ☐ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?
- Ingen spesiell tid 197 ☐ 1
- Særlig i mørketiden ☐ 2
- Særlig i midnattsoltiden ☐ 3
- Særlig vår og høst ☐ 4

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

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

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

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

LEGEMLIGE FUNKSJONER

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

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

Er du avhengig av noen av disse hjelpemidlene?

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

BRUK AV HELSEVESENET

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

	Antall ganger siste år
Hos vanlig lege/legevakt 228	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 234	_____
Innlagt i sykehus	_____
Hos fysioterapeut	_____
Hos kiropraktor 240	_____
Hos akupunktør	_____
Hos tannlege	_____
Hos fotterapeut 246	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

Har du hjemmehjelp?	Ja	Nei
Privat 252	☐	☐
Kommunal	☐	☐
Har du hjemmesykepleie?	☐	☐

Er du fornøyd med helse- og hjemmetjenesten i kommunen?

	Ja	Nei	Vet ikke
Prinsippet med fast lege 255	☐	☐	☐
Hjemmesykepleien	☐	☐	☐
Hjemmehjelpen	☐	☐	☐

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

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

LEGEMIDLER OG KOSTTILSKUDD

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

Legemidler

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

Kosttilskudd

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

FAMILIE OG VENNER

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

Hvis "Ja": Hvem kan gi deg hjelp?

- Ektefelle/samboer 294 ☐
- Barn ☐
- Andre ☐

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

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

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

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

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

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

KOSTVANER

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

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

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

	Loff	Flnt 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/uer)	☐	☐	☐	☐
– mager fisk (f.eks. torsk) 328	☐	☐	☐	☐
– grønnsaker (rå eller kokte)	☐	☐	☐	☐
Gulrøtter (rå eller kokte)	☐	☐	☐	☐
Blomkål/kål/brokkoli	☐	☐	☐	☐
Epler/pærer	☐	☐	☐	☐
Appelsiner, mandariner o.l. 333	☐	☐	☐	☐
	1	2	3	4

TRIVSEL

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

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

Hvordan ser du på livet fremover?

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

BESVARES BARE AV KVINNER

MENSTRUASJON

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

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

SVANGERSKAP

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

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

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

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

Hvis "Ja", i hvilket svangerskap?

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

ØSTROGEN-MEDISIN

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

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

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

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

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 syndrome	☐	☐
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

Do you cough daily for periods of the year? YES ☐ NO ☐

If "Yes":
Is your cough productive? YES ☐ NO ☐

Have you had this kind of cough for as long as 3 months in each of the last two years? YES ☐ NO ☐

Have you had periods of wheezing in your chest? YES ☐ NO ☐
If "Yes", has this occurred:
Tick one box only for each item.

	YES	NO
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? YES ☐ NO ☐

Have you lost weight in the last year? YES ☐ NO ☐
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 ☐

Do you suffer from:	No	A little	A lot
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?

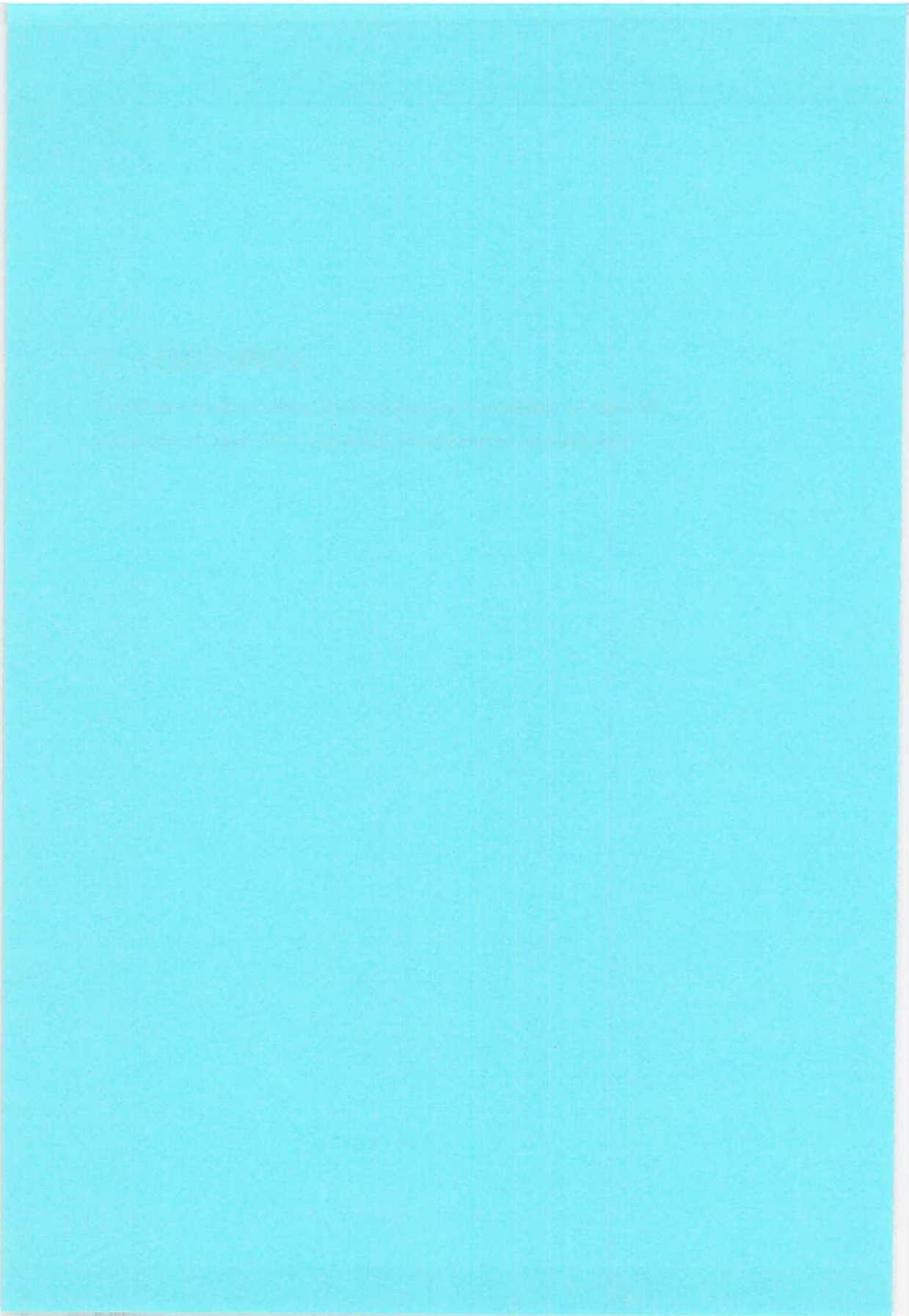
_____

Your comments:

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

APPENDIX E

Protocol for ultrasound measurements of intima-media thickness and recording and measurements of plaques of the right carotid artery



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 finding and clinical implications before leaving the room.

APPENDIX F

Protocol for scoring of ultrasound assessed plaque morphology

PROTOCOL FOR SCORING OF ULTRASOUND ASSESSED PLAQUE MORPHOLOGY. THE TROMSØ STUDY IV

by
Oddmund Joakimsen

ASSOCIATION BETWEEN PLAQUE MORPHOLOGY AND CLINICAL DISEASE?

Atherosclerotic lesions of the arterial wall manifest as so-called plaques. A plaque is defined as a localized, focal protrusion from the intima into the vessel lumen, often with a different appearance with regard to ultrasonographic density compared to adjacent parts of the vessel wall.

A plaque, which is growing to a certain size, will on predefined criteria (usually hemodynamic) be classified as a stenotic plaque causing a narrowing with significant hemodynamic disturbances of the blood flow.

Reports have recent years indicated that plaque echodensity (echogenicity) and heterogenity of stenotic plaques may be of significance as risk factors for cerebrovascular disease. Thus, low-echogenic (echolucent) plaques seem to be stronger associated to cerebrovascular disease than high-echogenic (echodense) plaques.[1;2] Few studies have reported the relation between the relation between nonstenotic plaques and cardio- or cerebrovascular disease.

The right carotid artery was examined by high-resolution ultrasound on approximately 7000 subjects in the fourth survey of the Tromsø Study in order to measure the intima-media thickness and atherosclerotic plaques. Plaque were recorded in the internal, common, and bifurcation part of the carotid artery, both from the near and far vessel wall - from 6 sites together. The maximum plaque thickness was measured on frozen ultrasound images of the respective sites. Number, localization, and maximum thickness from each plaque were recorded as three separate variables.

The video-recordings were stored which enabled subsequent analysis of two additional ultrasound variables: plaque echogenicity and plaque heterogeneity. The purpose was to explore any association between such plaque morphological features and clinical disease and cardiovascular risk factors.

On the videotapes, the recorded plaques, according to the protocol, are visualized in a full diameter of the vessel (i.e., "the greatest chord") (ideally, images with visible double-lined intima-media structures in both near and far walls). The plaque should in each end be "attached" to and continuous with the typical double-lined intima-media structures. Highest possible echogenicity was sought to achieve since, with a given setting of the instrument, falsely too high echogenicity is not possible to obtain, while falsely too low echogenicity is a usual finding of different reasons: Ultrasound beams may not hit the plaque perpendicularly, nonparallell vessel walls with the surface of the ultrasound transducer (causing nonoptimal conditions for echoreflection), the far wall plaque concealed by an "echoshadow" from a calcified near wall plaque due to inappropriate angling of the transducer against the neck, etc.

SCORING OF PLAQUE MORPHOLOGY

Visual scoring of plaque morphology necessarily is nothing more than a semiquantitative measurement procedure. It is not possible to standardize all aspects regarding recording and evaluation of plaques for obtaining objectively correct morphological characteristics. Emitted ultrasound intensity (power) and ultrasound gain and other instrument adjustments can not be completely standardized, and the amount of reflected ultrasound signals from different persons may vary due to other factors than echogenicity of the the vessel wall and plaque morphology. Several individual, biologic characteristics, such as distance from the skin to the vessel, differ because of different thickness of fat or muscle layers, individually different echogenicity of the vessel wall due to different pathoanatomic features, inter-individual variation in localization of the carotid bifurcation (high or low in the neck), the angle between the internal carotid artery upstream and the common carotid artery downstream, kinks and bends of the arteries, etc.

Ultrasound morphological reference structures therefore were used to enhance precision on morphology scoring and to getting round inter-individual differences. Thus, reflected signals from the far wall media-adventitia interface were used as the reference of high-echogenicity. This structure is easy to identify and is always presenting as high-echogenic, and is also localized close to the target, the atherosclerotic plaque, which is an advantage with regard to comparability. In a 4-step scale from 0 to 3, the media-adventitia echogenicity and plaques of similar echogenicity were given a value of 3. On a grey-scale, such objects appear white or close to white.

A plaque of grade 0 consequently reflects no or almost no ultrasound signals and appears black or dark grey on images. Flowing blood appearing black on ultrasound images is the reference structure on this end of the scale. Grade 1 and 2 represent intermediary echogenicity: grade 1, the plaque consisting of more echolucent than echogenic material; grade 2, more echogenic than echolucent. Apart from the ultrasound reference structures used in this protocol, the echogenicity scoring is similar to previous reports in the literature.[1;2]

Thus, plaque echogenicity is classified as follows:

Grade 0: Echolucent
Grade 1: Predominant echolucent
Grade 2: Predominant echogenic
Grade 3: Echogenic
Grade 4: Missing, not classifiable

Grade 4 represents plaques which are not possible to classify on ultrasound of technical reasons, e.g., plaques in the far wall concealed by the echoshadow from calcified near wall plaques, not possible to angling of the probe to obtain representative images, plaques localized to high upstream to get high-quality images, etc.

When a plaque is heterogenous and consists partly of low-echogenic and partly of high-echogenic material, the scoring of echogenicity is based on an overall impression of the dominating plaque morphology. When more than 80% of the plaque is of a given echogenicity the morphology is scored as if the whole plaque consisted of this echogenicity although the rest of the plaque morphology was differing 2 or 3 grades from the dominating class of echogenicity. If the percentage is below 80%, interpolating is performed by judgment. In the same way, a total echogenicity status for an artery is determined when more than one plaque is present. The same limit of 80% is the basis of scoring of total plaque area.

With regard to the heterogeneity of plaques, more than 80% of the classifiable plaque area should be of the same echogenicity to describe a plaque as homogeneous. If the echogenicity deviates only 1 grade from what is predominant in two thirds or more of the plaque area (including total plaque area if more than one plaque per artery), then "the plaque" still is defined as homogenous.

The correct values of echogenicity and heterogeneity are plotted in the form.

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APPENDIX G

Protocol for ultrasound measurement of carotid stenosis

PROCEDURES FOR ULTRASOUND RECLASSIFICATION AND CLINICAL EXAMINATION OF PERSONS WITH CAROTID STENOSIS. THE TROMSØ STUDY 1994/1995

By Oddmund Joakimsen

BACKGROUND

The Tromsø Study 1994/1995 is a population study organized in to separate visits. All inhabitants of the municipality of Tromsø aged 25 and over, are asked to participate in the first visit comprising measurements of blood pressure, height and weight, etc. They fill in a questionnaire about previous and current diseases, dietary habits, modes of living, etc. The collection of data started in August 1994 and is supposed to be finished one year later.

Those who attend the first visit and were in agegroups of 55-74 years, and 5-10% samples of other 5-year agegroups, altogether approximately 7000 persons, will be invited to the second visit. At the second visit, following examinations will be done: ultrasound of the aorta and the heart, extensive electrocardiography, blood pressure measurements, blood and urine sampling, bone density measurements, and others. The second visit also comprises ultrasound examination of the right carotid artery in the neck. The purpose of the examination is to investigate, as described in a detailed procedure protocol[1], the morphological and hemodynamic conditions of the right carotid artery by the use of high-resolution B-mode and colour-Doppler/pulsed wave Doppler ultrasound technology.

The subjects who are suspected to have carotid stenosis according to predefined criteria[1] and age-and-sex matched controls will be invited to further ultrasound investigation and reclassification and also offered a full clinical examination at Department of Neurology, University Hospital, Tromsø. The more detailed background and purpose of this stenosis arm of Tromsø Study IV are presented in a separate protocol[2].

In the following, a short description of the investigations that cases and control persons will undergo, is presented. Further and more detailed presentations of the ultrasound procedures are described in the procedural protocol[1] and in the protocol for classification of plaque morphology[3].

INVESTIGATION PROCEDURES

In general, the follow-up variables will consist of relevant elements of the medical history, clinical data obtained by clinical examination, and various data from the ultrasound examinations (size and localization of stenotic plaques, plaque morphology, and hemodynamic values). All data will be recorded in a registration form and given separate ID-numbers exclusive for each subject.

Medical history

Cerebrovascular episodes

Previous episodes of transient ischemic attacks (TIA), cerebral ischemic strokes, transient monocular blindness (amaurosis fugax), or retinal infarcts are recorded. Number of such episodes and time (in months) since last event are noted together with presumed cerebral localization of a TIA-episode or an ischemic stroke. A RIND (reversible ischemic neurologic deficit lasting more than 24 hours, but no longer than 21 days) is in this context defined as an ischemic stroke.

Syncope

Syncope is defined as sudden loss of consciousness due to a global cerebral blood hypoperfusion caused by extra-cerebral mechanisms. Number of syncopes in the preceding year, and time for last episode are registered.

Angina pectoris

Angina pectoris is defined as selfreported or medical record documented coronary insufficiency symptoms provoked by usual mechanisms (physic or psychic stress). Yes/no response is recorded.

Myocardial infarction

Myocardial infarction is defined as selfreported or medical record documented previous myocardial infarction. Time for the last infarction (if more than one) is recorded together with a specification of where in the myocard the infarction occurred (for evaluation of the risk of cardiogenic cerebral embolization).

Arterial vascular insufficiency of legs

This is defined as exercise-induced pain in the legs (calves) typically provoked by walking (claudicatio intermittens). Yes/no response is recorded.

Clinical status

According to a standardized protocol completed for each participant, clinical neurologic symptoms and signs were recorded following a modified long-term "Scandinavian Stroke Scale" investigation programme. Blood pressure in both arms and bruits in the neck and supraclavicularly are recorded.

ULTRASOUND EXAMINATIONS

Traditional ultrasound examinations used in neurological practice consist of Doppler or colour-Doppler/duplex ("triplex") examinations of the carotid and vertebral arteries extracranially in order to detect stenosis, occlusion, or other abnormal flow patterns (e.g., subclavian steal phenomenon). Sometimes, additional examinations such as collateral flow conditions through the orbit or transcranial Doppler/triplex examinations are performed from clinical indication, but not as a routine. To a lesser extent, B-mode examinations for demonstration of plaque presence, size, and morphology have normally been used, although factors such as plaque echogenicity and heterogeneity have shown to be potential independent risk factors for ischemic stroke.[4-8] It was therefore decided to score plaque morphology of stenotic plaques in the same way as plaques scored in the primary ultrasound screening at the fourth survey of the Tromsø Study.[3]

The dynamic examinations aim to investigate velocities over the stenosis and distally in the internal carotid artery (reference velocity). In addition, presence and "size" of vortex/backflow upstream a stenosis also are registered and measured, if possible. The angle of the jet of the blood across a stenosis against the vessel wall upstream will be measured, this procedure and the rationale behind are also defined in detail in the procedural protocol.[2] Presence and direction of flow in the vertebral arteries will be registered.

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