# Trends in prevalence of ultrasound-assessed carotid atherosclerosis in a general population over time. The Tromsø Study 1994-2016.

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## Abstract

**Background:**

During the past decades, there has been a shift in risk factor levels in many high-income countries, with decrease in smoking, blood pressure and cholesterol levels, while body mass index, obesity and diabetes increase. The diverging trends may have opposite effects on prevalence of atherosclerosis. We aimed to assess carotid plaque prevalence and the association with risk factor levels in a general population over a period of 22 years.

**Methods:**

Prevalence of plaque, number of plaques and total plaque area in the carotid arteries were assessed in three repeated cross-sectional surveys of the population-based Tromsø Study from 1994 through 2016. The number of participants from the first to the last survey was 6362, 7069 and 3021. All surveys included physical examinations, questionnaires, and blood samples. Multivariable logistic regression analysis models were fitted to assess the relationship between risk factors and carotid plaque.

**Results:**

We found no significant change in plaque burden over a period of 22 years, neither when measured as plaque presence, plaque number or total plaque area. Plaques were more frequent in men (70%) than in women (59.4%) and increased by age. Systolic blood pressure and smoking increased, while BMI and diabetes decreased over time both in participants with and without plaque. Most risk factors remained higher in participants with plaque than in plaque-free participants while cholesterol levels decreased and reached similar levels in both groups. Age, male sex, systolic blood pressure, smoking, diabetes and HDL cholesterol (inverse) were associated with plaque prevalence.

**Conclusions:**

Plaque prevalence remained stable in the observation period. Favorable reductions in systolic blood pressure, cholesterol and smoking may have been partly counteracted by increased diabetes prevalence. Risk factor levels remained higher in participants with plaque than in plaque-free participants, indicating a potential for further improvement in primary prevention of carotid atherosclerosis.

## Introduction

Cardiovascular disease (CVD) is a leading cause of death and disability. Atherosclerosis is the dominant underlying cause of a majority of CVD, including coronary heart disease, stroke, and peripheral vascular disease. During the last decades, the incidence of both myocardial infarction and ischemic stroke has declined in many high-income countries,[1,2] in parallel to a shift in CVD risk factor levels, towards decreasing trends in blood pressure levels, cholesterol levels and smoking prevalence.[3-5] On the other hand, body mass index, obesity, and diabetes have increased.[6-7] These diverging trends in risk factor levels may have had opposite effects on prevalence of subclinical and clinical CVD.

Carotid artery atherosclerosis as assessed by ultrasound correlates well with the level of atherosclerosis elsewhere in the arteries,[8-9] and is associated with future risk of myocardial infarction and ischemic stroke.[10-14] It may be assumed that the reduced incidence of myocardial infarction and ischemic stroke has been mediated by a concomitant reduction in the prevalence of subclinical atherosclerotic plaques; however, this has not been clearly documented in population-based studies. In a recent systematic review and meta-analysis, the worldwide prevalence of carotid plaque was estimated to 21% in people aged 30–79 years, equivalent to approximately 816 million people.[15] However, reports on prevalence of carotid atherosclerotic plaques in population-based studies from countries with decreasing CVD incidence show diverging results, with estimates ranging from 13% to 93%.[12, 16-32] Despite efforts to reach a standardized definition of a carotid plaque through the Mannheim consensus,[33] methodology and definition of carotid plaques varies between studies and make comparisons of carotid plaque prevalence complicated.

In the Tromsø Study, plaque prevalence has been estimated in repeated cross-sectional surveys of the general adult population over a period of 22 years, a period where significant reductions in the incidence of myocardial infarction and ischemic stroke in the population have taken place.[1,2] The aim of the present study was to assess the current plaque prevalence in the population and to assess whether change in risk factor levels over time has led to a concomitant reduction in the prevalence of carotid plaque.

## Materials and methods

### Study population

The Tromsø Study is a single-centre population-based prospective study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway.[34] A total of seven cross-sectional screening surveys have so far been carried out with 6-8-year intervals from 1974 until 2016. All surveys have included a basic physical examination, questionnaires, and blood samples (first visit). From the fourth survey and onwards, selected age cohorts and random samples were invited to a second visit with a more extensive examination, including ultrasound examination of the carotid arteries. The surveys were conducted by the University of Tromsø.

The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics, North Norway (REK Nord 2009/2536-3, REK Nord 2014/940) and the Norwegian Data Inspectorate. The study adheres to the tenets of the Declaration of Helsinki. All participants gave written, informed consent. The participants are free to withdraw their consent at any time, and to give new consent later, for example when participating in a new survey. Thus, the number of participants with valid written consent from each survey may vary over time.

Eligible for the present study were all 3027 subjects aged 40-84 years who attended the carotid ultrasound examination of the 7th survey (Tromsø 7) conducted in 2015-2016. One participant was excluded due to lack of valid written consent. We also excluded participants missing ultrasound images (n=5) and with missing information on plaque status in the right carotid artery (n=10). Thus, 3011 participants were included in the present study. A more detailed description and flow chart are presented in the Supplemental Material.

For comparison of prevalence and risk factor levels over time, we included information from participants of the carotid ultrasound examination of the 4$^{th}$ survey (Tromsø 4) conducted in 1994-95 and the 6$^{th}$ survey (Tromsø 6) conducted in 2007-2008. Data from the ultrasound examination from the 5th survey was not included because this was a follow-up of previous participants of 4th survey, meaning that any change in plaque prevalence would most likely be due to ageing. In the 4th survey, carotid ultrasound examination of the right carotid artery was performed in 6727 subjects. Subjects who did not consent to medical research (n = 42),

and a group of high-risk men included via a sub-survey (n = 323) were excluded, leaving 6362 subjects who were included in the analyses (Supplemental Figure 1). In the 6th survey, 7084 underwent carotid ultrasound examination of the right carotid artery. Subjects who did not consent to medical research (n = 2) or had missing ultrasound images (n = 13) were excluded, leaving 7069 subjects who were included in the analyses (Supplemental Figure 2). Details about the attendance for each of the surveys are presented in the Supplemental Material.

**Cardiovascular risk factors**

Assessments of risk factors were done according to the same protocol in the three surveys. Information about smoking habits (never, former, current), prevalent diabetes mellitus, cardiovascular disease, and use of medication were collected from self-administered questionnaires, checked by trained nurses. Height and weight were measured in light clothing without shoes. Body mass index (BMI) was calculated as weight per squared height (km/m2). Obesity was defined as BMI ≥ 30. Diabetes mellitus was defined as self-reported diabetes mellitus and/or HbA1c ≥ 6.5%. Blood pressure was recorded by use of an automatic device (Dinamap Vital Signs Monitor) in a separate, quiet room by a specially trained nurse a. After the participants had been seated for 2 minutes, three recordings were made at 2-minute intervals. The mean of the two last recordings were used in the present analyses. Hypertension was defined as self-reported hypertension and/or self-reported use of blood pressure lowering drugs and/or a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg. Non-fasting serum total cholesterol were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol; Boehringer-Mannheim). All analyses were performed at the Department of Clinical Chemistry, University Hospital of Tromsø.

**Ultrasound examination**

The same scanning procedures were used in all surveys. In the 4th survey high-resolution B-mode ultrasonography was performed with a duplex scanner (Acuson Xp10 128, ART-upgraded) equipped with a 7.5 MHz linear array transduce. In the 6th and 7th survey, a GE Vivid duplex scanner with a linear 12 MHz transducer was used. Details about the ultrasound

methods and the intra- and interobserver and inter-equipment reproducibility have been published previously.[35-36] Only the right carotid artery was examined in Tromsø 4 and 6, while both carotid arteries were examined in Tromsø 7.

The far- and near walls of the right common carotid artery (CCA), bifurcation (bulb) and internal carotid artery (ICA) (6 locations) were scanned for the presence of plaques. A plaque was defined as a focal structure in the intima-media layer with protrusion into the arterial lumen of more than 50% of the surrounding intima–media thickness (IMT), measured from the media–adventitia interface to the intima–lumen interface. The number of plaques in each carotid artery was registered and documented with still images of each plaque. The area of each plaque was outlined manually with automatic calculation of plaque area. In Tromsø 4 and 6, measurements of plaque area were done off-line, while this was done on-line in Tromsø 7. In subjects with more than 1 plaque, the areas of all plaques were summarized to give the total plaque area (TPA).

**Statistical methods**

Characteristics of participants with and without plaque were summarised using means or proportions (%) with 95% confidence intervals. Prevalence of plaque is reported as proportions (%) with 95% confidence intervals. TPA is reported as median (interquartile range).

For comparison of plaque frequency in the right and left artery in Tromsø 7, we excluded participants with missing information on plaque number in one of the arteries (n = 135). As only the right carotid artery was examined in Tromsø 4 and 6, we included Tromsø 7 participants with information on plaque in the right carotid artery for analyses of plaque prevalence and TPA over time, regardless of whether data were available for the left artery or not.

Multivariable logistic regression analysis models were fitted to assess the relationship between risk factors and carotid plaque, with plaque (yes/no) as the dependent variable and age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, current daily smoking, BMI, and diabetes mellitus as independent variables.

Statistical analyses were performed using Stata statistical software (version 17: Stata Corp)[37]. Two-sided p values lower than 0.05 were considered significant.

## Results

Baseline characteristics of Tromsø 7 participants are shown in Table 1. Mean age of participants were 64.1 years (range 40-84 years), and 54% were males. Women had a significantly lower prevalence of previous stroke and coronary heart disease compared to men. Women also had significantly lower mean blood pressure values, a lower prevalence of hypertension and diabetes, lower mean BMI and higher values of HDL- and total-cholesterol compared to men.

The overall prevalence of plaque in one or both carotid arteries was 64.2% (Table 2). Plaques were more frequent in men than in women. The prevalence increased by age from 21.9 % in the youngest age group to 87.9 % in the oldest age group in men and from 14% to 82.5 % in women. The prevalence tended to be higher in the left carotid artery than in the right (52.4%, 95 % CI 50.6-54.2 vs 50.7%, 95% CI 48.8-52.5), but the differences were not significant.

The age- and sex-specific prevalence of plaques in the right carotid artery in each of the three surveys are shown in Table 3. In men, prevalence was 9.5% (95% CI 6.0-14.1) and 13.7% (95% CI 6.8-23.8) in the youngest age-group in 4$^{th}$ and 7$^{th}$ survey, and 82.4% (95% CI 65.5-93.2) and 77.5% (95% CI 72.1-82.3) in the oldest age-group. In women, prevalence was 7.4% (95% CI 4.7-11.0) and 8.4% (95% CI 3.7-15.9) in the youngest age-group in 4$^{th}$ and 7$^{th}$ survey, and 80.4% (95% CI 66.1-90.6) and 71.4% (95% CI 65.8-76.7) in the oldest age-group. The number of plaques in the right carotid artery was similar in all surveys (Supplemental Table 1).

The age- and sex-specific median TPA in the right carotid artery in each of the three surveys are shown in Table 4. TPA increased by age and was larger in men than in women in all age groups. There were no significant differences in TPA between surveys.

Mean systolic blood pressure on average decreased by approximately 10 mmHg in the observation over the 22 years period, most pronounced in women (Figure 1, Supplemental

Figure 3, Supplemental Table 2). There was also a substantial reduction in cholesterol levels and smoking prevalence across surveys. Between 1994 and 2008, the prevalence of diabetes increased from 2.8% to 6.0% in subjects without plaque and from 5.6% to 11.2% in those with plaque, while BMI increased by approx. 1 kg/m$^2$ in both groups.

In the 4$^{th}$ survey, age, male sex, systolic blood pressure, total cholesterol, HDL cholesterol (inverse), smoking and diabetes were independently associated with plaque prevalence (Table 5). In the 7$^{th}$ survey, cholesterol was no longer significantly associated with plaque, while the estimated risks associated with diabetes (OR 1.75, 95% CI 1.26-2.42 vs. 1.36, 95% CI 1.02-1.83) and smoking (OR 1.83, 95% CI 1.42-2.36 vs. 1.62, 95% CI 1.43-1.84) were higher compared to 22 years earlier.

## Discussion

In the present study, we found that the overall carotid plaque prevalence in the most recent survey of our population was 64.2%. Plaques were more frequent in men than in women and increased by age. We found no significant change in plaque burden over a period of 22 years, neither when measured as plaque presence, plaque number or total plaque area. Systolic blood pressure, cholesterol levels and smoking decreased over time, while there was an increase in BMI and prevalent diabetes. Cholesterol levels, which in previous surveys were associated with increased risk of carotid plaque, was no longer significantly associated with plaque presence, while the estimated odds ratios for diabetes and smoking were higher compared to 22 years earlier.

Plaque prevalence varies considerably in recent population-based studies from high-income Western countries (Table 6).[12, 16-26] Our results are fairly similar to the prevalence found in the BioImage Study[20] conducted in 2008-2009, the Wisconsin Sleep Cohort study[22] conducted between 2004-2012 and the Beaver Dam Studies[26] conducted between 1998 and 2000. A high plaque prevalence of 87% was reported in the recent population-based Norwegian ACE (Akershus Cardiac 1950 Examination) Study.[17] In contrast, plaque prevalence was 25% in a Swedish study of 65-year-old males[21] and 27% in the Greek Corinthia Study.[16] Differences in population demographics and risk factor levels may have contributed to some of the variation, but it is difficult to find a consistent pattern in these factors which can explain the relatively

large differences between studies. For example, the age and sex distribution in the Corinthia Study and the Swedish study was similar to our study, as was the gender distribution and mean age of participants in the ACE study, although with a narrower age range of 63-65 years. Methodological differences in assessment and definition of plaques may also explain some of differences between studies. Most, but not all, studies used a definition of plaque according to the Mannheim Consensus.[33] The majority reported plaque prevalence as a combination of plaques in the CCA, bulb, and ICA (Table 6). The Corinthia Study reported plaque prevalence from the ICA only, while the ACE Study included plaques in the external carotid artery, which may have contributed to the lower and higher plaque prevalence in these studies, respectively. Variation in technical equipment, standards for image acquisition and other methodological variations may also have influenced results.

Plaques tended to be more frequent in the left carotid compared to the right carotid in both men and women, although not significantly. Adams et al. reported that carotid artery atherosclerosis is a symmetrical disease, and presence of atherosclerosis in one carotid makes it more likely to have atherosclerosis in the opposite carotid.[38] Selwaness found that although most individuals had plaques in both carotid arteries, unilateral plaque was more often located in the left carotid artery and that left-sided plaques were thicker than right-sided plaques.[39]

We found that systolic blood pressure, cholesterol levels and smoking decreased significantly over time, both in plaque-free participants and participants with plaque and in men and women, while BMI and prevalent diabetes increased. Risk factor levels continued to be higher in participants with plaque throughout the period, except for cholesterol, where mean levels declined more steeply in the plaque group in the first part of the observation period to reach the same levels as in the plaque-free group in 2007-2008 and 2015-2016. This was reflected in the multivariable-adjusted logistic regression analysis, where cholesterol no longer was significantly associated with plaque presence. The use of lipid-lowering medication increased considerably from almost no use in 1994 to 28.5% in 2016. The main explanatory factor for the decrease in cholesterol is thought to be dietary change with reduction in the intake of saturated fat and trans-fat and higher consumption of poly-unsaturated fats and fish oil.[40]

The estimated odds ratio for diabetes was higher in the last survey compared to 22 years earlier and comparable to the results from the recent meta-analysis by Song and coworkers.[15] Our results regarding the association between systolic blood pressure and smoking and plaque

as well as the lack of significant association between BMI and plaque were also in line with the results from the meta-analysis.[15]

In light of the reduction systolic blood pressure, cholesterol and smoking and the fact that the incidence of cardiovascular disease decreased significantly in the Tromsø population in the same period, it is surprising that we found no change in plaque prevalence over time. This may to a certain extent have been counteracted by an unfavorable increase in diabetes. It is also possible that cohort effects may have influenced results, due to altered risk factor patterns in the birth cohorts which attended the last survey (eg, psychosocial stress, dietary and other life style changes) which we have been unable to account for.

Although a favorable decline in systolic blood pressure, cholesterol levels and smoking were seen in both participants with plaque and in plaque-free persons, the risk factor levels continued to be higher in participants with plaque. This underlines the need for continued efforts to improve primary prevention of carotid atherosclerosis.

**Strengths and limitations**

Strengths of our study include the population-based design with repeated cross-sectional measurements over time in a well-defined large population, which allows analyses of trends in prevalence and risk factors over time. The same ultrasound screening protocols were used in all three surveys. The study also has several limitations. Different ultrasound equipment was used in the 4$^{th}$ and 6$^{th}$/7$^{th}$ survey, and this may have facilitated detection of plaques in the latter surveys. Plaques were measured only in the right carotid artery in the two first surveys, which limits the trend analyses to measurements from the right carotid. Our study was conducted in a high-income, developed country and the results cannot be conferred to other regions. The population consisted mainly of Caucasians and the generalizability to other race and ethnic groups is therefore unknown.

**Conclusions**

We found no significant change in carotid plaque prevalence over a period of 22 years, neither when measured as plaque presence, plaque number or total plaque area. Plaques were more frequent in men than in women and increased by age. There was a favorable shift in systolic blood pressure, cholesterol levels and smoking decreasing over time, while BMI and diabetes increased. While risk factor levels decreased in both participants with plaque and in

plaque-free persons, systolic blood pressure, HDL cholesterol, BMI, smoking, and diabetes continued to be higher in participants with plaque than in those without plaque. This indicates that continued efforts aimed at reduction of risk factors in the general population may improve primary prevention of carotid atherosclerosis.

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**Table 1. Characteristics of participants*. The 7th survey of the Tromsø Study, 2015-2016**

| | Men | Women | Total* |
|---|---|---|---|
| No. of subjects, n (%) | 1319 (45.7) | 1567 (54.3) | 2886 (100) |
| Mean age, years | 64.5 (63.9-65.1) | 63.8 (63.2-64.3) | 64.1 (63.7-64.5) |
| Systolic blood pressure, mm Hg | 135.5 (134.5-136.5) | 132.7 (131.6-133.8) | 134.0 (133.2-134.7) |
| Diastolic blood pressure, mm Hg | 77.5 (77.0-78.0) | 72.9 (72.4-73.4) | 75.0 (74.6-75.4) |
| Hypertension, % | 58.7 (55.9-61.4) | 50.0 (47.4-52.5) | 54.0 (52.1-55.8) |
| Serum total cholesterol, mmol/L | 5.26 (5.20-5.31) | 5.66 (5.61-5.72) | 5.48 (5.44-5.52) |
| Serum HDL cholesterol, mmol/L | 1.43 (1.41-1.46) | 1.79 (1.76-1.81) | 1.63 (1.61-1.65) |
| Use of lipid-lowering drugs, % | 31.1 (28.6-33.7) | 26.3 (24.1-28.6) | 28.5 (26.9-30.2) |
| Current smoking, % | 11.9 (10.2-13.8) | 12.9 (11.3-14.7) | 12.5 (11.3-13.7) |
| Diabetes mellitus, % | 9.4 (7.9-11.1) | 6.9 (5.6-8.3) | 8.0 (7.1-9.1) |
| Coronary heart disease, % | 12.1 (10.4-14.0) | 3.4 (2.5-4.5) | 7.7 (6.7-8.8) |
| Previous stroke, % | 4.5 (3.5-5.8) | 2.3 (1.6-3.1) | 3.3 (2.7-4.0) |
| Body mass index, $kg/m^2$ | 27.6 (27.4-27.8) | 26.7 (26.4-26.9) | 27.1 (27.0-27.3) |
| Obesity, % | 20.7 (18.7-22.8) | 22.4 (20.2-24.7) | 21.5 (20.0-23.0) |

Numbers are means or proportions with 95% confidence intervals.

HDL; high density lipoprotein

Coronary heart disease was defined as previous myocardial infarction and/or previous or current angina

*Participants with missing plaque assessments in one or both carotid arteries were excluded from the analyses

**Table 2. Prevalence (%) of plaques in the right and left carotid arteries*, stratified by age group and sex. The 7th survey of the Tromsø Study, 2015-2016**

| Age groups, years | Men (n=1319) | | | | | | Women (n=1567) | | | | | | Total (n=2886) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **<45** (n=73) | **45-54** (n=183) | **55-64** (n=344) | **65-74** (n=469) | **≥75** (n=250) | **All** (n = 1319) | **<45** (n=93) | **45-54** (n=237) | **55-64** (n=436) | **65-74** (n=538) | **≥75** (n=263) | **All** (n = 1567) | |
| **Right carotid** | 13.7 (6.8-23.8) | 24.0 (18.1-30.9) | 53.8 (48.4-59.1) | 66.5 (62.1-70.8) | 76.8 (71.1-81.9) | 56.3 (53.6-59.0) | 8.6 (37.9-16.3) | 19.4 (14.6-25.0) | 36.5 (31.9-41.2) | 59.3 (55.0-63.5) | 71.1 (65.2-76.5) | 45.9 (43.4-48.4) | 50.7 (48.8-52.5) |
| **Left carotid** | 12.3 (5.8-22.1) | 23.0 (17.1-29.7) | 54.7 (49.2-60.0) | 71.4 (67.1-75.5) | 78.4 (72.8-83.3) | 58.4 (55.7-61.1) | 7.5 (3.1-14.9) | 20.3 (15.3-25.9) | 43.8 (39.1-48.6) | 55.2 (50.9-59.5) | 75.7 (70.0-80.7) | 47.4 (44.9-49.9) | 52.4 (50.6-54.2) |
| **Both carotids†** | 21.9 (13.1-33.1) | 35.5 (28.6-42.9) | 68.0 (62.8-72.9) | 82.9 (79.2-86.2) | 87.9 (82.9-91.4) | 70.0 (67.4-72.4) | 14.0 (7.7-22.7) | 31.2 (25.4-37.5) | 55.7 (50.9-60.5) | 71.4 (67.4-75.2) | 82.5 (77.4-86.9) | 59.4 (56.9-61.9) | 64.2 (62.5-66.0) |

*Participants with missing plaque assessments in one or both carotid arteries were excluded from the analyses

†Plaque in the right, left and/or both carotid arteries

**Table 3. Prevalence (%) of plaque in the right carotid artery in the 4th, 6th and 7th survey of the Tromsø Study, by sex and age-group**

| | Men | | | | | Women | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age groups** | **<45** | **45-54** | **55-64** | **65-74** | **≥75** | **<45** | **45-54** | **55-64** | **65-74** | **≥75** | |
| **Tromsø 4** | 9.5 | 37.9 | 53.3 | 69.6 | 82.4 | 7.4 | 18.2 | 41.3 | 62.1 | 80.4 | 50.3 |
| | (6.0-14.1) | (30.0-46.4) | (50.7-55.8) | (66.7-72.3) | (65.5-93.2) | (4.7-11.0) | (13.1-24.3) | (38.8-43.9) | (59.5-64.8) | (66.1-90.6) | (49.1-51.6) |
| **Tromsø 6** | 16.7 | 33.0 | 46.0 | 62.2 | 74.3 | 6.9 | 25.0 | 35.5 | 49.7 | 69.8 | 46.5 |
| | (6.4-32.8) | (28.7-37.4) | (43.3-48.8) | (58.8-65.5) | (69.9-78.4) | (2.3-15.5) | (21.7-28.6) | (33.2-37.9) | (46.7-52.7) | (65.9-73.5) | (45.4-47.7) |
| **Tromsø 7** | 13.7 | 24.6 | 53.5 | 66.9 | 77.5 | 8.4 | 19.3 | 36.1 | 59.7 | 71.4 | 51.2 |
| | (6.8-23.8) | (18.6-31.4) | (48.2-58.8) | (62.6-71.1) | (72.1-82.3) | (3.7-15.9) | (14.6-24.9) | (31.6-40.8) | (55.5-63.8) | (65.8-76.7) | (49.4-53.0) |

Numbers are percentages (95% confidence intervals)

**Table 4. Total plaque area* in the right carotid artery in the 4th, 6th and 7th survey of the Tromsø Study, by sex and age-group**

| | Men | | | | | | Women | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age groups** | **<45** | **45-54** | **55-64** | **65-74** | **≥75** | **Total men** | **<45** | **45-54** | **55-64** | **65-74** | **≥75** | **Total women** | |
| **Tromsø 4** | 9.5 (7) | 12 (12) | 16 (17) | 22 (26) | 35 (43) | 18 (22) | 9 (7) | 7 (7) | 11.5 (13) | 16 (18) | 21 (23) | 13.5 (15) | 16 (18.5) |
| **Tromsø 6** | 19 (13) | 17 (20) | 19 (18) | 26 (27) | 34 (35) | 23 (24.5) | 8 (6) | 12 (13) | 14.5 (15) | 18 (18.5) | 24 (24) | 17 (17.5) | 20 (22) |
| **Tromsø 7** | 10 (6) | 10.5 (9) | 17 (17) | 22 (23) | 27 (34) | 20 (24) | 10.5 (15) | 10 (7) | 12.5 (11.5) | 14 (16) | 19 (25.5) | 14 (17) | 17 (20) |

Numbers are median (interquartile range) in $mm^2$

*In participants with plaque(s)

**Table 5. Multivariable logistic regression analysis of association between cardiovascular risk factors and plaque prevalence in the 4th and 7th surveys of the Tromsø Study**

| | Tromsø 4 (1994-1995) | | Tromsø 7 (2015-2016) | |
|---|---|---|---|---|
| | **Odds ratio** | **95% CI** | **Odds ratio** | **95% CI** |
| Mean age, years | 1.09 | 1.08-1.09 | 1.08 | 1.07-1.09 |
| Male sex | 1.62 | 1.44-1.83 | 1.42 | 1.19-1.69 |
| Systolic blood pressure, per 10 mmHg | 1.10 | 1.07-1.13 | 1.14 | 1.09-1.19 |
| Serum total cholesterol, mmol/L | 1.21 | 1.16-1.27 | 1.04 | 0.96-1.13 |
| Serum HDL cholesterol, mmol/L | 0.72 | 0.62-0.82 | 0.70 | 0.57-0.85 |
| Current smoking, % | 1.62 | 1.43-1.84 | 1.83 | 1.42-2.36 |
| Diabetes mellitus, % | 1.36 | 1.02-1.83 | 1.75 | 1.26-2.42 |
| Body mass index, $kg/m^2$ | 0.98 | 0.97-1.00 | 1.00 | 0.98-1.02 |

CI; confidence interval, HDL; high density lipoprotein

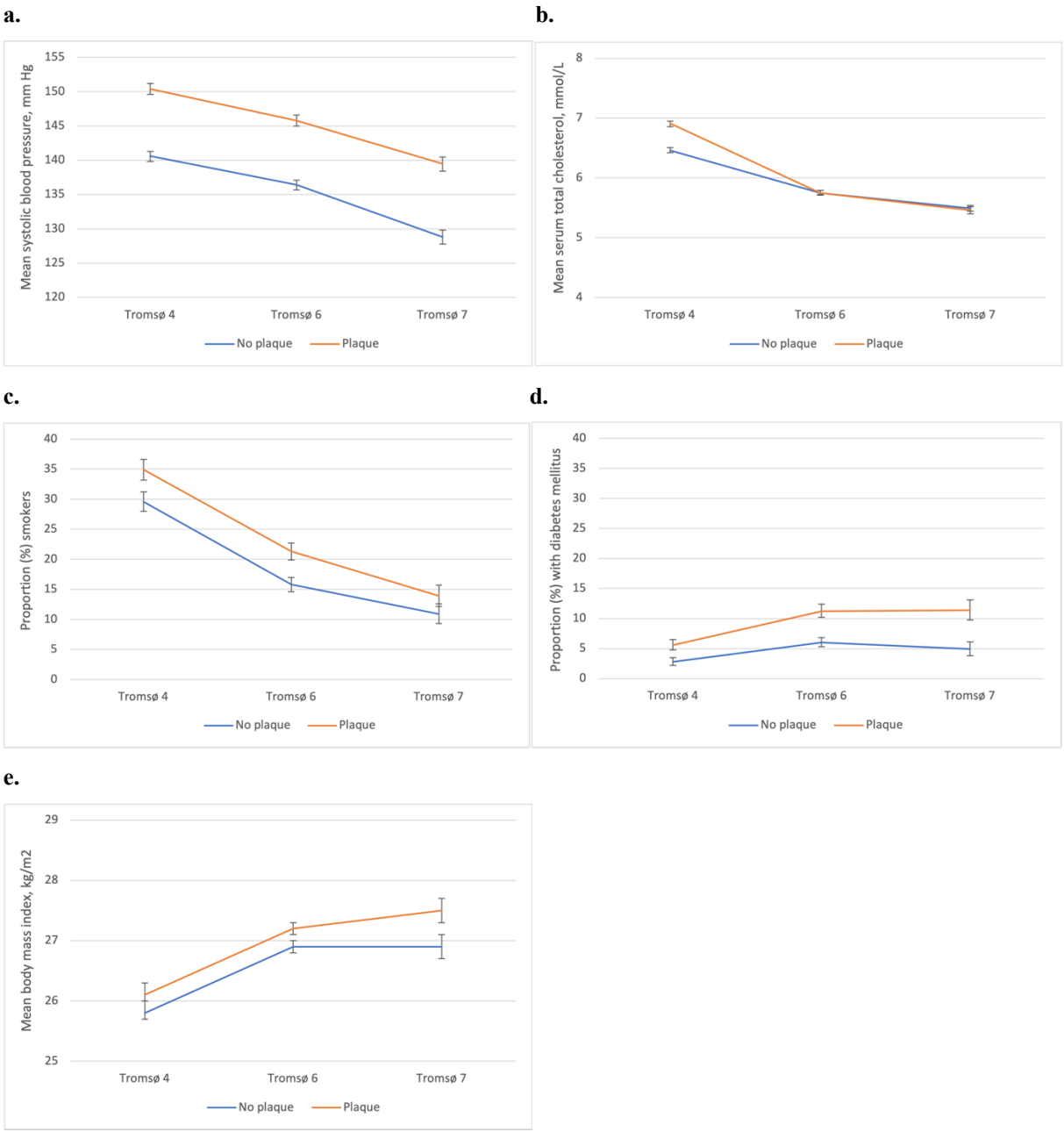
**Table 6. Prevalence of ultrasound-assessed plaques in population-based studies**

| Study | Years conducted | Characteristics | Carotid sites | Definition of plaque | Plaque prevalence |
|---|---|---|---|---|---|
| Tromsø 7 | 2015-2016 | N 2886; 54.3% women<br>Mean age 64.1, range 40-84 years | CCA, bulb, ICA | Focal protrusion of ≥ 50 % of the surrounding IMT | 64% |
| Corinthia study | 2015-2017 | N 2043; 60% women<br>Mean age 64±12 | CCA, bulb, ICA, ECA | Focal thickening ≥ 50 % of the surrounding IMT or IMT > 1.5 mm | 27% |
| ACE | 2012-2015 | N 3683; 49% women<br>Mean age 63.9±0.7, range 63-65 | CCA, bulb, ICA, ECA | Focal protrusion of ≥ 0.5 mm or ≥ 50 % of the surrounding IMT value or IMT > 1.5 mm | 87% |
| Dahl et al. | 2011-2013 | N 1474, women only<br>Age range 61-76 | CCA, bulb, ICA, ECA | Focal protrusion of ≥ 0.5 mm or ≥ 50% of the surrounding IMT | 41% |
| REFINE | 2005-2011 | N 6524; 51% women<br>Mean age 49.7±11.2, range 25-69 | Bulb, ICA | Isolated thickening at least two times the adjacent normal IMT by visual assessment | 45 % |
| BioImage Study | 2008-2009 | N 5,808; 57% women<br>Mean age 68.9±6 | CCA, bulb, ICA | Focal protrusion of ≥ 0.5 mm or 50% of the surrounding IMT or IMT >1.5 mm | 58% |
| Högberg et al. | 2007-2009 | N 4657; men only<br>All aged 65 | Internal carotid artery | Focal intimal-media thickening of ≥ 2 mm, over at least 6 mm of length | 25% |
| Wisconsin Sleep Cohort | 2004-2012 | N 790; 44% women<br>Mean age 47.6 | CCA, bulb, ICA | Focal structure with protrusion of ≥ 50 % of the surrounding IMT value or IMT > 1.5 mm | 63% |
| Beaver Dam Offspring Study | 2005–2008 | N 2,302; 54% women<br>Mean age 49, range 21-84 | CCA, bulb, ICA | 1) Acoustic shadowing associated with i) protrusion into the lumen or ii) a change in wall texture or iii) IMT > 1.5 mm, or<br>2) In the absence of acoustic shadowing: presence of at least two of the characteristics above | 24% |
| PIVUS | 2001-2005 | N 931; 50% women<br>All aged 70 | CCA, bulb, ICA | Focal thickening ≥ 50 % of the surrounding IMT | 29% |
| MESA | 2000-2002 | N 3310, 53% women<br>Mean age 60.3 | CCA, bulb, ICA | Focal thickening of > 50% of the surrounding IMT or IMT >1.5 mm | 47% |
| Beaver Dam Studies | 1998-2000 | N 1700; Mean age, 66.8, range 53-96 | CCA, bulb, ICA | 1) Acoustic shadowing associated with protrusion into the lumen or a change in wall texture or IMT > 1.5 mm, or<br>2) In the absence of acoustic shadowing: presence of at least two of the characteristics above | 67% |

| | | | | | |
|---|---|---|---|---|---|
| NOMAS | 1999-2001 | N 1790; 60% women<br>Mean age 69±9 | CCA, bulb, ICA | Focal thickening ≥ 50 % of the surrounding IMT | 58% |
| British Regional Heart Study | 1996 | N 800; 47% women<br>Mean age 66, range 56-77 | CCA, bulb, ICA | Localized thickening >1.2 mm that did not uniformly involve the whole left or right common carotid bifurcation with or without flow disturbance | 56% |
| ARIC | 1993-1995 | N 1343 (641 Blacks and 702 Whites)<br>Mean age 63 | CCA, bulb, ICA | Focal IMT >1.5 mm, or a hyperechoic region with luminal protrusion | Blacks 35%<br>Whites 40% |
| Rotterdam Study | 1990-1993 | N 4217; 60% women<br>Mean age 68.8 | Right CCA, bulb, ICA | Focal protrusion of >50% relative to adjacent segments (visual assessment) | 60% |
| San Daniele project | 1989-1990 | N 1348; 53% women<br>Age range 18-99 | CCA, bulb, ICA | Distinct area with either mineralization or focal protrusion into the lumen | 13% |
| Finnish cohort of the Seven Countries Study | 1989 | N 182; women only<br>Mean age 75.9, range 70-89 | CCA, bulb | 1) Nonmineralized lesion: uneven arterial wall surface or a luminal protrusion or IMT > l.5 mm<br>2) Mineralization: presence of an echogenic shadow | Nonmineralized 51%<br>Mineralized 91 % |
| ARIC | 1987-1989 | N 14,046; 55% women<br>Age range 45-64 | CCA, bulb, ICA | Two of the following three conditions:<br>(1) Protrusion into the lumen, loss of alignment with adjacent arterial boundary, no roughness of the arterial boundary<br>(2) Brighter echoes than adjacent boundaries<br>(3) IMT >1.5 mm | 34% |

ACE; Akershus Cardiac Examination 1950 Study, REFINE; Risk Evaluation For INfarct Study, PIVUS; Prospective Study of the Vasculature in Uppsala Seniors Study, MESA; Multi-Ethnic Study of Atherosclerosis, NOMAS; Northern Manhattan Study, ARIC; Atherosclerosis risk in Communities Study

**Figure 1. Riskfactor levels in participants with and without carotid plaque in in the 4th, 6th and 7th survey of the Tromsø Study**




Blue lines represent participants without carotid plaque, orange lines participants with carotid plaque. Vertical bars show 95% confidence intervals.

Panel a: mean systolic blood pressure (mmHg), b: mean cholesterol levels (mmol/L), c: proportion of daily smoker (%), d: proportion with diabetes (%), e: mean body mass index (kg/m$^2$)

# SUPPLEMENTAL MATERIAL

**Trends in prevalence of ultrasound-assessed carotid atherosclerosis in a general population over time. The Tromsø Study 1994-2016.**

## Materials and methods

*Study population*

The fourth survey of the Tromsø Study started in September 1994 and was completed in October 1995. The survey comprised two screening visits 4 to 12 weeks apart. All inhabitants aged 25 years and above living in the municipality of Tromsø were invited to the 1st visit, and 27 158 subjects attended (77% of invited). Those invited to the 2nd visit were all 1st visit participants aged 55-74 years, 5-10% samples of participants aged 25-54 years and 75-85 years, as well as a selected group of 340 high-risk men aged 40-54 years who in the 1979-80 survey had total cholesterol values in the highest decile and/or HDL cholesterol in the lowest quintile. A total of 6902 subjects attended (76% of the invited) and 6727 participated in the carotid ultrasound examination of the right carotid artery. For the purpose of this paper, we excluded 323 of the 340 high-risk men aged 40-54 years, while 17 men who were part of the randomized sample of 5% were included. We further excluded 42 participants without valid written consent to medical research (n = 42). The final number included in the present paper was 6362 participants (Supplemental Figure 1).

Tromsø 6 was carried out from 1 October 2007 to 19 December 2008. A total of 19 762 subjects aged 30–87 years were invited and 12 984 subjects attended (66% of the invited). All 1st visit participants aged 50-62 and 75-84 years, a 20% random sample of 1st visit participants aged 63-74 years and participants who had previously taken part in the 2nd visit in the 4th survey and were aged <75 years in 1994, were invited to the 2nd visit examination. A total of 7307 subjects attended the 2nd visit (64% of invited), and carotid ultrasound examination of the right carotid artery was performed in 7084 subjects. Subjects without valid written consent (n = 2) and subjects with missing information of plaque number (n = 13) were excluded, leaving 7069 subjects who were included in the analyses from the 6th survey (Supplemental Figure 2).

All Tromsø inhabitants aged 40 and above (n = 32 591) were invited to the first visit of the 7th survey and 21 083 attended (65%). A premarked subsample of 13 028 subjects, consisting of a random sample (76%) and previous participants of the 2nd visit of the 6th survey (24%), was eligible for the 2nd visit, of whom 50% were eligible for carotid ultrasound examination. A total of 8346 subjects attended the second visit (64% of the eligible). The main survey took place from March 2015 through Nov 2016, while the carotid ultrasound examinations, for logistic reasons, started 5 months later (17 August 2015). A total of 3027 subjects attended the carotid ultrasound examination, which comprised assessment of both right and left carotid

arteries. Participants with missing images (n=5) or with lack of information on plaque status in the right carotid artery (n=10) were excluded. This was done in order to compare the results with data from the 4th and 6th survey. Furthermore, we excluded one participant without valid written consent. Thus, 3011 participants of from the 7th survey were included in the study (Supplemental Figure 3).

**Supplemental Table 1. Number of plaques in the right carotid artery in the 4th, 6th and 7th survey of the Tromsø Study**

| | Plaque number | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** | **5** | **6** | |
| **Tromsø 4** | 49.7 (3160) | 29.6 (1884) | 14.1 (894) | 4.4 (282) | 1.7 (107) | 0.5 (29) | 0.1 (6) | 100 (6362) |
| **Tromsø 6** | 53.5 (3780) | 26.8 (1894) | 14.8 (1045) | 4.0 (283) | 0.8 (57) | 0.1 (10) | 0 (0) | 100 (7069) |
| **Tromsø 7** | 48.8 (1470) | 28.2 (848) | 18.4 (553) | 3.8 (114) | 0.7 (22) | 0.1 (4) | 0 (0) | 100 (3011) |

Numbers are percentages (n).

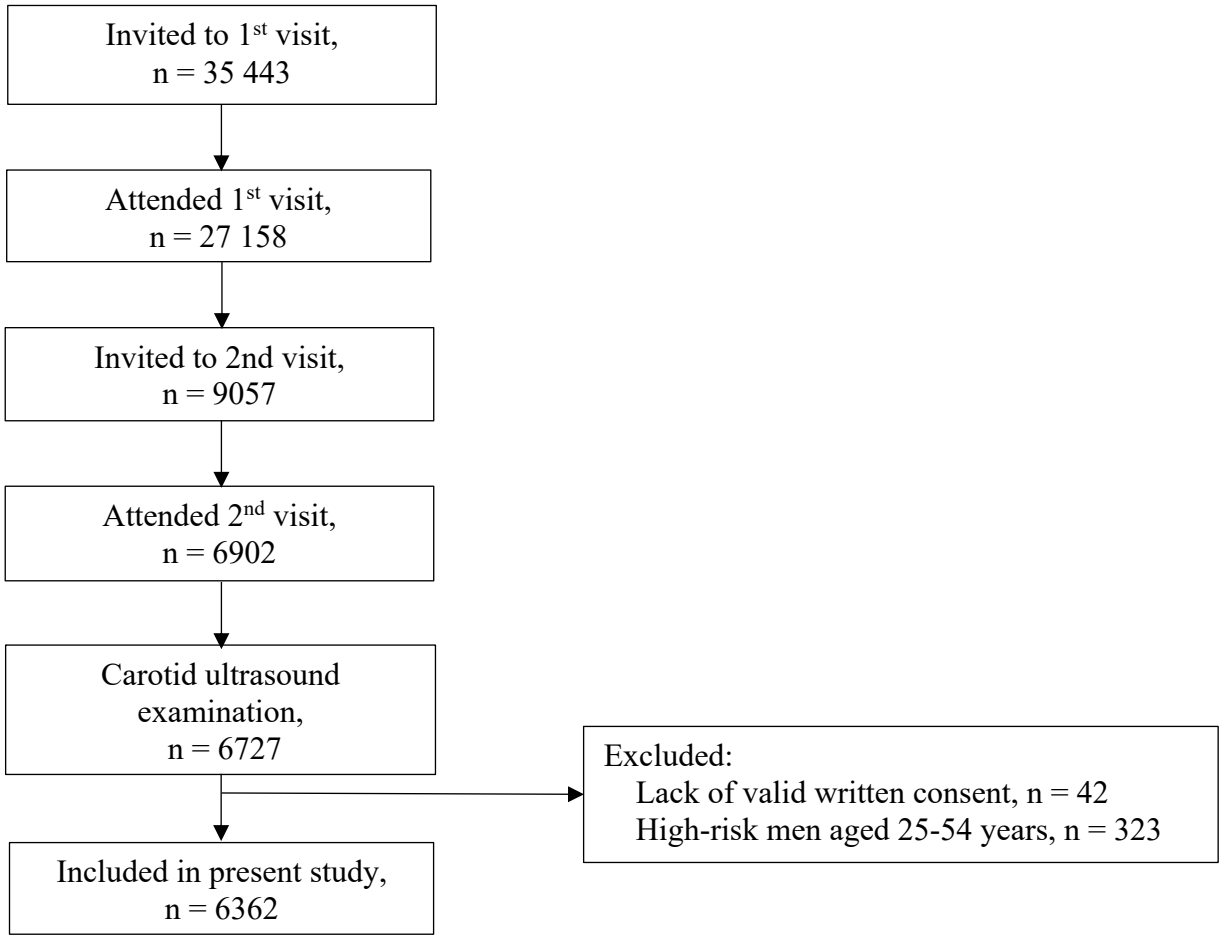
**Supplemental Table 2. Baseline characteristics of participants of the 4th, 6th and 7th survey of the Tromsø Study, 2015-2016**

| | Tromsø 4 | | Tromsø 6 | | Tromsø 7 | |
|---|---|---|---|---|---|---|
| | **No plaque** (n = 3160) | **With plaque** (n = 3202) | **No plaque** | **With plaque** | **No plaque** | **With plaque** |
| Male sex, n (%) | 1325 (44.4) | 1659 (55.6) | 1464 (48.0) | 1589 (52.0) | 595 (43.0) | 789 (57.0) |
| Mean age, years | 57.1 (56.7-57.5) | 64.3 (64.1-64.6) | 61.1 (60.8-61.3) | 66.5 (66.2-66.8) | 59.9 (59.4-60.5) | 68.5 (68.0-68.9) |
| Systolic blood pressure, mmHg | 140.6 (139.8-141.3) | 150.4 (149.6-151.2) | 136.4 (135.7-137.1) | 145.8 (145.0-146.6) | 128.8 (127.8-129.8) | 139.5 (138.4-140.5) |
| Diastolic blood pressure, mmHg | 81.8 (81.3-82.2) | 84.8 (84.3-85.2) | 78.1 (77.8-78.4) | 78.9 (78.5-79.3) | 74.5 (74.0-75.0) | 75.6 (75.1-76.1) |
| Serum total cholesterol, mmol/L | 6.5 (6.4-6.5) | 6.9 (6.9-7.0) | 5.8 (5.7-5.8) | 5.8 (5.7-5.8) | 5.5 (5.4-5.5) | 5.5 (5.4-5.5) |
| Serum HDL-cholesterol, mmol/L | 1.6 (1.5-1.6) | 1.5 (1.5-1.5) | 1.6 (1.6-1.6) | 1.5 (1.5-1.5) | 1.7 (1.6-1.7) | 1.6 (1.6-1.6) |
| Current smoking, n (%) | 29.6 (28.0-31.2) | 34.9 (33.2-36.6) | 15.8 (14.6-17.0) | 21.3 (19.9-22.7) | 10.9 (9.3-12.6) | 13.9 (12.2-15.7) |
| Diabetes mellitus, n (%) | 2.8 (2.2-3.5) | 5.6 (4.8-6.5) | 6.0 (5.3-6.8) | 11.2 (10.2-12.4) | 4.9 (3.8-6.1) | 11.4 (9.8-13.1) |
| Body mass index, $kg/m^2$ | 25.8 (25.7-26.0) | 26.1 (26.0-26.3) | 26.9 (26.8-27.0) | 27.2 (27.1-27.3) | 26.9 (26.7-27.1) | 27.5 (27.3-27.7) |

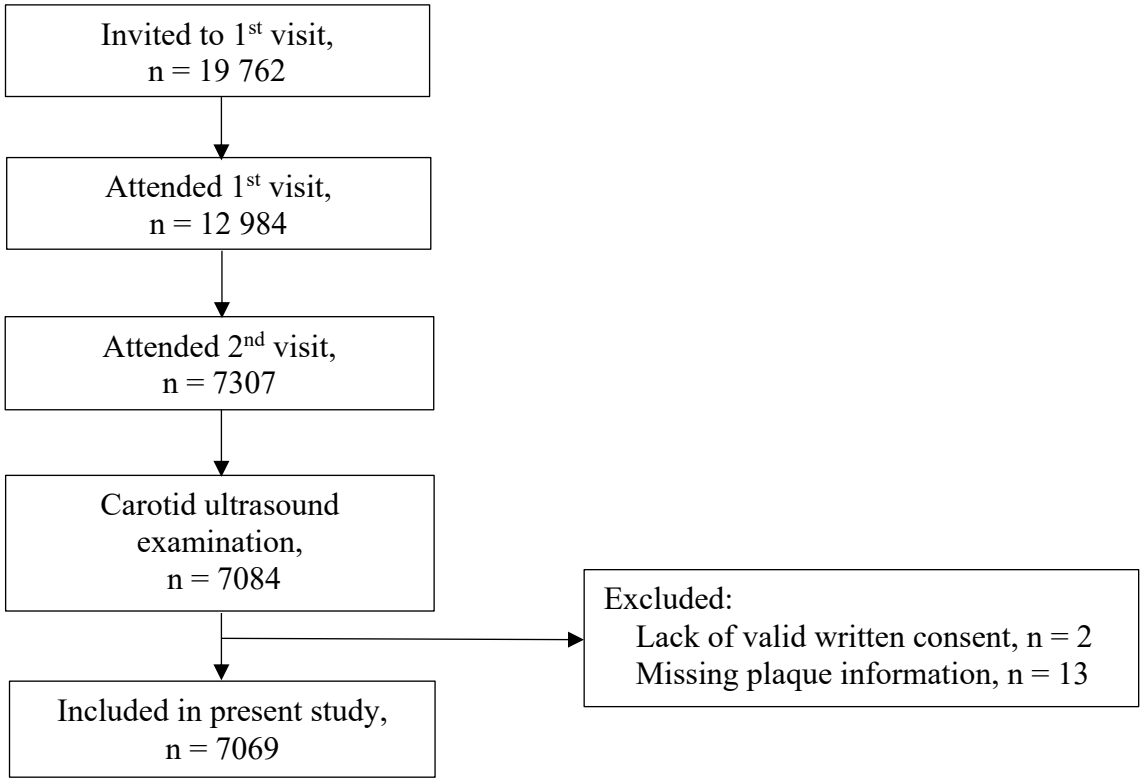
Numbers are means or proportions with 95% confidence intervals.

HDL; high density lipoprotein

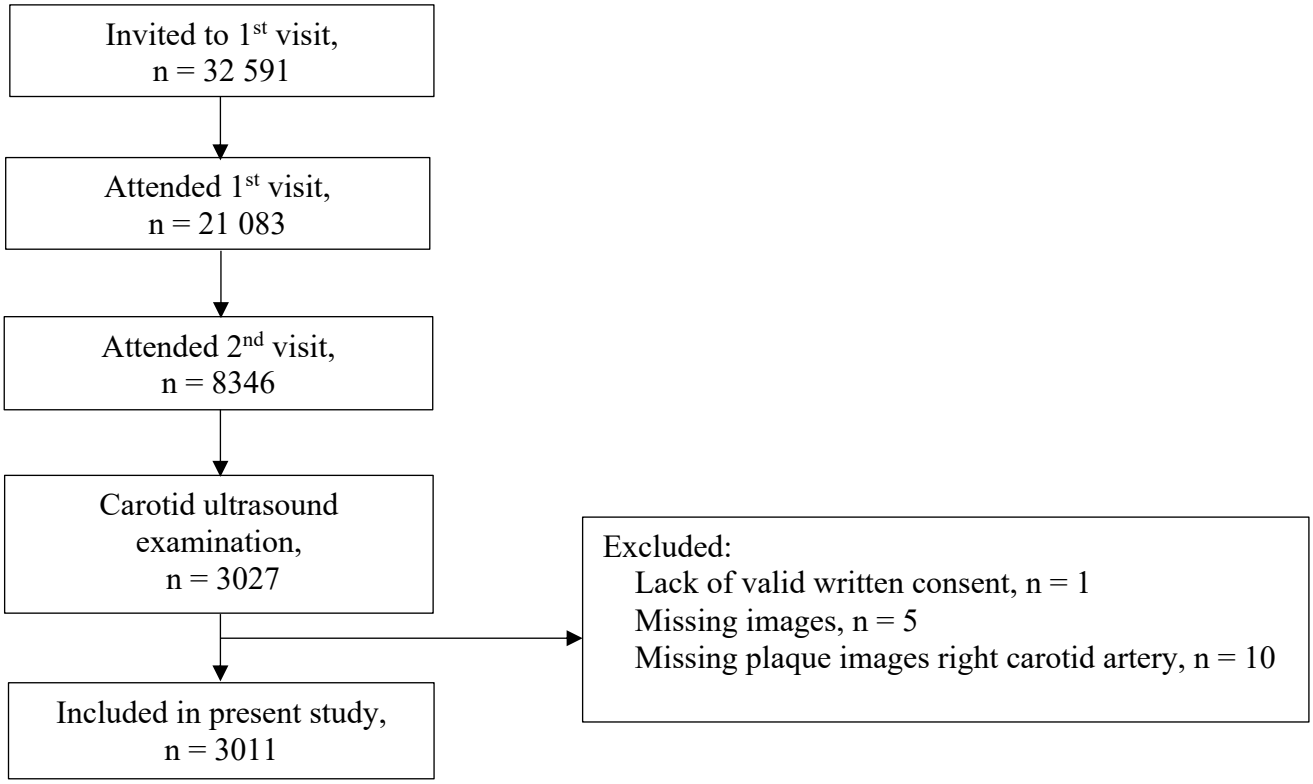
**Supplemental Figure 1. Flow chart of participants of the 4th survey of the Tromsø Study (1994-1995)**



**Supplemental Figure 2. Flow chart of participants of the 6th survey of the Tromsø Study (2007-2008)**

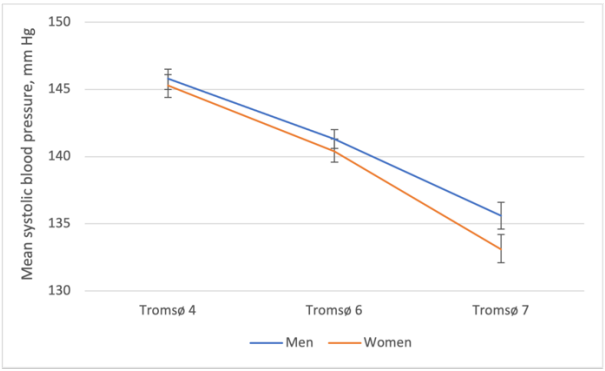


**Supplemental Figure 3. Flow chart of participants of the 7th survey of the Tromsø Study (2015-2016)**



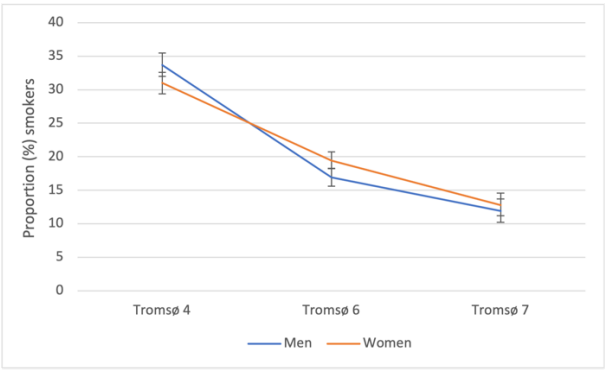
**Supplemental Figure 4. Risk factor levels in participants of the 4th, 6th and 7th survey of the Tromsø Study, by sex**

**a.**

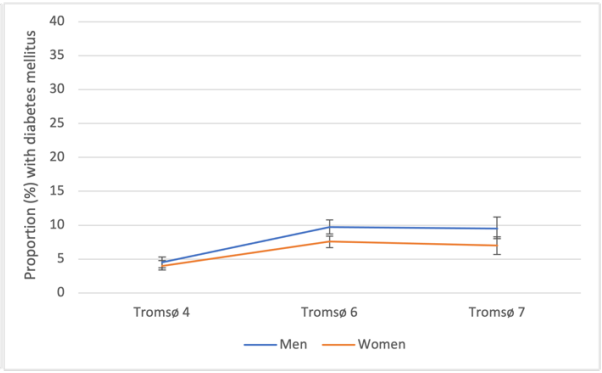



**b.**

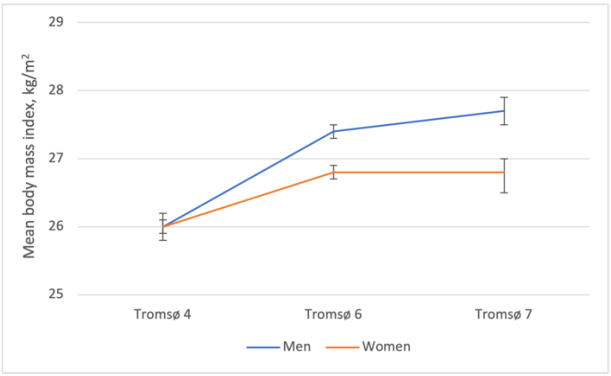

**c.**




**d.**




**e.**




Blue lines represent men, orange lines women. Vertical bars show 95% confidence intervals.

Panel a: mean systolic blood pressure (mmHg), b: mean cholesterol levels (mmol/L), c: proportion of daily smoker (%), d: proportion with diabetes (%), e: mean body mass index (kg/m$^2$)