ORIGINAL RESEARCH

Prevalence of Carotid Plaque in a 63- to 65-Year-Old Norwegian Cohort From the General Population: The ACE (Akershus Cardiac Examination) 1950 Study

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***Background*—**New data on extracranial carotid atherosclerosis are needed, as improved ultrasound techniques may detect more atherosclerosis, the definition of plaque has changed over the years, and better cardiovascular risk control in the population may have changed patterns of carotid arterial wall disease and actual prevalence of established cardiovascular disease. We investigated the prevalence of atherosclerotic carotid plaques and carotid intima–media thickness (cIMT) and their relation to cardiovascular risk factors in a middle-aged cohort from the general population.

***Methods and Results*—**We performed carotid ultrasound in 3683 participants who were born in 1950 and included in a population-based Norwegian study. Carotid plaque and cIMT were assessed according to the Mannheim Carotid Intima–Media Thickness and Plaque Consensus, and a carotid plaque score was used to calculate atherosclerotic burden. The participants were aged 63 to 65 years, and 49% were women. The prevalence of established cardiovascular disease was low (10%), but 62% had hypertension, 53% had hypercholesterolemia, 11% had diabetes mellitus, and 23% were obese. Mean cIMT was 0.73±0.11 mm, and atherosclerotic carotid plaques were present in 87% of the participants (median plaque score: 2; interquartile range: 3). Most of the cardiovascular risk factors, with the exception of diabetes mellitus, obesity and waist–hip ratio, were independently associated with the plaque score. In contrast, only sex, hypertension, obesity, current smoking, and cerebrovascular disease were associated with cIMT.

***Conclusions*—**We found very high prevalence of carotid plaque in this middle-aged population, and our data support a greater association between cardiovascular risk factors and plaque burden, compared with cIMT.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01555411. **(*J Am Heart Assoc*. 2018;7: e008562. DOI: 10.1161/JAHA.118.008562.)**

Key Words: atherosclerosis • cardiovascular disease • carotid artery • carotid ultrasound

Atherosclerosis is a systemic disease that affects the vascular system and that develops gradually over years, initially as a thickening of the vessel wall and slowly developing into an atherosclerotic formation.[1]

B-mode ultrasound examination of the carotid artery is an effective and validated noninvasive method to assess the degree of atherosclerosis and subclinical disease. Both carotid intima–media thickness (cIMT) and carotid plaque have been used as surrogate markers of atherosclerosis and cardiovascular disease (CVD). Traditionally, cIMT is thought to represent the first structural change in the atherosclerotic process, likely to progress to an atheroma located in the carotid wall. Among all ultrasound measures, the total plaque area (the sum of all plaque areas) as a marker for plaque

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Clinical Perspective

What Is New?

- Carotid plaque was found in nearly 9 of 10 participants aged 63 to 65 years in this population-based study.
- Traditional cardiovascular risk factors were common in participants with carotid plaque, and we found a strong association between cardiovascular risk factors and carotid plaque burden.

What Are the Clinical Implications?

- When performing ultrasound examination of the carotid arteries in participants aged 63 to 65 years, carotid plaque will be a frequent finding.
- Our findings support previous data suggesting that assessment of carotid plaque burden may be more useful than measuring carotid intima–media thickness in cardiovascular risk stratification.

burden has been shown to be the strongest predictor of future cardiovascular events.[2]

Previous reports regarding the prevalence of carotid plaque and cIMT thickness are scarce and of older date.[3–5] New and improved ultrasound techniques enhance atherosclerosis detection and thus may influence the measured plaque prevalence. In addition, increased awareness and treatment of modifiable risk factors may have affected the prevalence of subclinical vascular disease.

The aim of this study was to explore the prevalence of subclinical atherosclerotic carotid disease, measured with ultrasound in a large cohort from the Norwegian population aged 63 to 65 years, and the associations with cardiovascular risk factors.

Methods

The data set used in this study is not publicly available; the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information is available on the study website (http://www.ace1950.no).

The ACE (Akershus Cardiac Examination) 1950 study is a prospective, population-based, cohort study of the cerebrovascular and cardiovascular health of all men and women born in 1950 in Akershus County, Norway. The design of the study was published previously.[6] In short, at the baseline visit, all participants underwent an interview, clinical examination, fasting blood samples, and advanced imaging. The participants were examined at one of the 2 hospitals in the county (Akershus University Hospital or Bærum Hospital, Vestre Viken Health Trust).

Medical History and Lifestyle Variables

Hypertension was defined as an average measurement of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg in sitting position after 10 minutes of rest and/or use of antihypertensive medication. Diabetes mellitus was defined as HbA1c ≥6.5% and/or fasting plasma glucose ≥7.0 mmol/L and/or use of glucose-lowering medication. Obesity was defined according to the World Health Organization definition (body mass index [kg/m^2] ≥30).[7] Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L and/or low-density lipoprotein ≥4.1 mmol/L[8] and/or use of lipid-lowering medication. History of stroke or transient ischemic attack, CVD, smoking habits, and level of physical activity were self-reported. Higher education was defined as >12 years of formal education. Systemic Coronary Risk Evaluation (SCORE) was used to calculate the cardiovascular risk in the study population.[9]

B-Mode Ultrasound Recordings of the Carotid Artery

Ultrasound images of the right and left extracranial arteries (common carotid artery, internal and external carotid artery) were recorded in both long- and short-axis views on a Vivid E9 machine (GE Healthcare) using a linear L9 array transducer for vascular imaging. The cIMT was measured in B-mode using a semiautomated IMT package for the Vivid E9 system. The measurements were conducted over a minimum of 10-mm length on both sides at the far wall in the common carotid artery, longitudinal and perpendicular to the ultrasound beam, in lateral view, at least 5 mm proximal of the bifurcation in an area with clearly defined lumen–intima and in a region free of plaque. The mean average cIMT was used (Figure 1).[10]

A plaque was defined according to the latest version of the Mannheim Carotid Intima–Media Thickness and Plaque Consensus: a focal structure that protrudes into the arterial lumen of at least 0.5 mm or 50% of the surrounding cIMT value or that demonstrates a thickness of 1.5 mm measured form the media–adventitia interface.[11]

The carotid artery was divided into 4 segments (common carotid artery, bifurcation, and internal and external carotid artery), and plaques were assessed in each segment.[12] The diameter of the greatest plaque in each segment was measured. Plaque diameters ≥1.5, ≥2.5, and ≥3.5 mm were given 1, 2, and 3 points, respectively (Figure 2). The point scores for each of the 4 segments were summarized into a total plaque burden score, ranging from 0 to 24 points.[12] Plaque assessment was performed blinded to medical history status and cardiovascular risk profile.

Carotid artery stenosis severity was assessed in accordance with Consensus Panel gray scale and Doppler US criteria[13]; peak velocity <125 cm/s was considered normal,

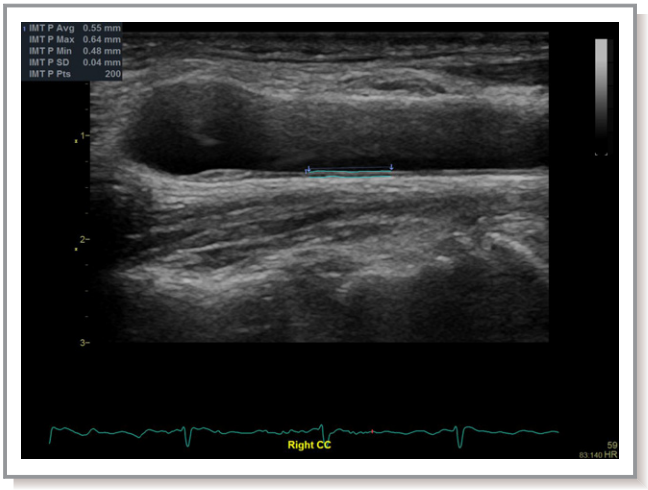

Figure 1. Carotid intima–media thickness (cIMT). The cIMT was measured in B-mode, longitudinal view, using a semiautomated IMT package for the Vivid E9 system. The measurements were conducted over a minimum 10-mm length, at the far wall in the common carotid artery (CC), at least 5 mm proximal of the bifurcation in an area with clearly defined lumen–intima and in a region free of plaque. The mean average cIMT was used (0.55 mm in this example). IMT, indicates intima–media thickness.

125 to 230 cm/s showed 50% to 69% stenosis, and >230 cm/s showed >70% stenosis.

The examinations were performed by 2 ultrasound technicians and 2 physicians, all trained in vascular ultrasound, and all underwent a joint training program before the start of the study. All analyses were performed offline on Echopac PC v12 (GE Vingmed) by the 2 physicians. Inter- and intrarater reliability tests were performed twice during the inclusion period, in which the 2 physicians measured plaque diameter twice for plaque score calculation on the same 25 randomly selected examinations. Both tests showed excellent results (Cronbach κ=0.999).

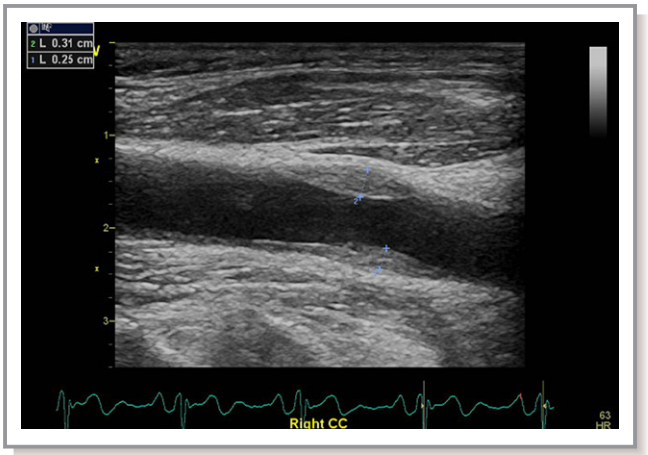

Figure 2. Plaque formation located in the right common carotid (CC) artery. For calculation of the carotid plaque burden, the carotid artery was divided in 4 segments (common carotid artery, bifurcation, and internal and external carotid artery), and plaques were assessed in each segment. The largest plaque from every segment was measured. Plaque diameters ≥1.5, ≥2.5, and ≥3.5 mm were given 1, 2, and 3 points, respectively, with a segment score of 2 (diameter of the largest plaque: 3.1 mm) for the right common carotid artery in this participant. Finally, the scores from all segments were summarized into a total plaque burden score ranging from 0 to 24 points.

Ethics

The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway (ref. number 2011/1475). All participants signed written informed consent before entering the study.

Statistical Analysis

Descriptive demographic and clinical measures are shown as mean±SD or as numbers and percentages. The cIMT is given as mean±SD, plaque score is shown as median and interquartile range, and prevalence is shown as percentages with 95% confidence intervals (score with continuity correction; Fleiss quadratic). The independent-samples Student *t* test was used for comparisons between groups. Categorical variables were compared using the χ^2 test. Distribution of plaque burden was assessed in relation to risk burden using percentiles. The impact of clinical variables on plaque score was analyzed using Poisson regression, because the plaque scores were approximately Poisson distributed (Figure 3), whereas linear regression was used to assess the impact of clinical variables on cIMT, as cIMT was approximately normally distributed. Variables with $P \leq 0.1$ in univariate analyses were included in the multivariate analyses. The significance level was set at $P<0.05$ in the multivariate analysis. All analyses were performed using IBM SPSS Statistics 23 software.

Results

After inviting 5827 participants, a total of 3706 were included in the ACE 1950 study (attendance rate 64%). One had missing values because of technical and anatomical difficulties and 22 declined to take part in the ultrasound survey, leaving 3683 participants with complete carotid ultrasound examinations (Figure 4). The participants were aged 63 to 65 years (mean: 63.9±0.7 years), and 1887 (51%) were male. Clinical characteristics are shown in Table 1.

Atherosclerotic carotid plaques were present in 87% of the participants. The median plaque score was 2 (interquartile range: 3). The most frequent plaque localization was carotid bulb, present in 83% of the participants. Plaque was more often present in men than women (92% versus 83%, $P<0.001$). The prevalence of >50% carotid artery stenosis was 2.3% in the total cohort, with no significant sex differences (2.6% in

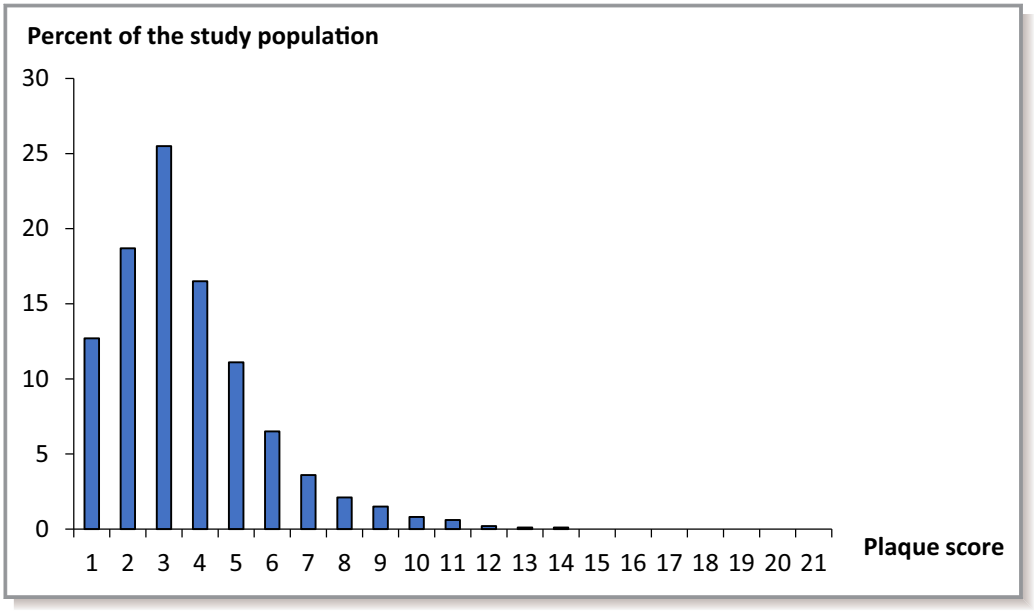

Figure 3. Plaque score distribution.

men versus 1.9% in women, *P*=0.228). Ultrasound characteristics are shown in Table 2.

Increasing plaque scores were associated with increasing burden of traditional cardiovascular risk factors. An overview of the prevalence of cardiovascular risk factors in the different plaque categories is presented in Table 3. Participants with a plaque score in the fourth quarter (with a plaque score ≥4), compared with participants with scores in the first 3 quarters (with a plaque score <4), had a significantly higher prevalence of hypertension, hypercholesterolemia, diabetes mellitus, obesity, current smoking, CVD, and cerebrovascular disease. Furthermore, the proportion of high and very high 10-year risk of fatal CVD according to SCORE was significantly higher in the fourth quarter compared with the first 3 quarters. In addition, these participants also had significantly lower prevalence of higher education and physical activity.

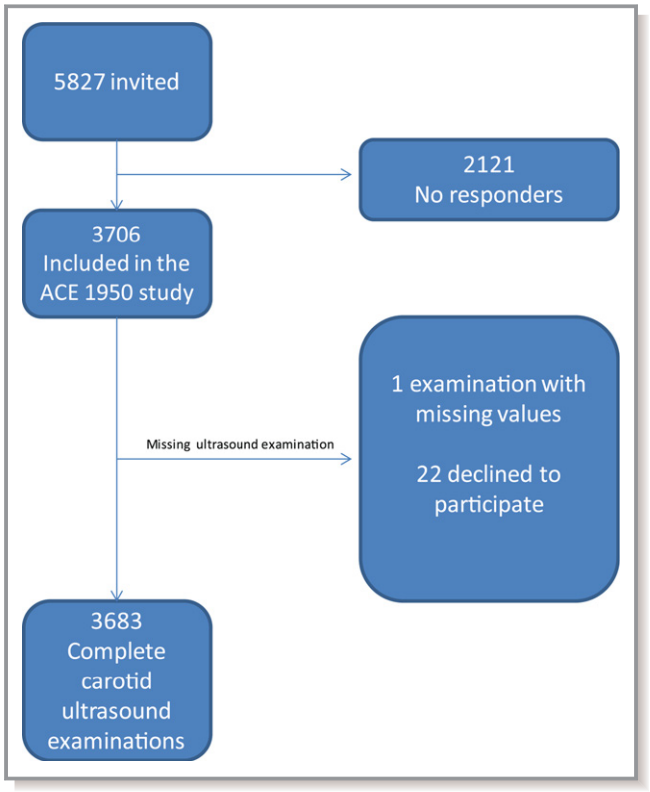

Figure 4. Flowchart of the ACE (Akershus Cardiac Examination) 1950 study population.

The following variables were associated with higher plaque scores in both univariate and multivariate analysis: current smoking, hypertension, coronary heart disease, history of cerebrovascular disease, hypercholesterolemia, and physical inactivity. In contrast, female sex and higher education were associated with lower plaque scores (Table 4). The model explained 16% of the total variation of the plaque score (r^2=0.16).

Mean cIMT was 0.73±0.11 mm. In univariate analyses, male sex, diabetes mellitus, hypertension, current smoking, obesity, waist–hip ratio, coronary heart disease, and history of cerebrovascular disease were associated with cIMT. In multivariate analysis, in descending order of impact, only sex, cerebrovascular disease, hypertension, obesity, and current smoking were independently associated with cIMT (Table 5). The model explained only 5% of the total variation of cIMT (r^2=0.05).

Discussion

The early stages of carotid artery vessel pathology are highly visible in a general middle-aged population: Carotid plaques were present in 9 of 10 participants aged 63 to 65 years in

Table 1. Baseline Characteristics of the Study Population

Variable	Total (n=3683)	Men (n=1887)	Women (n=1796)
Sex	100	51	49
Hypertension	62	66	58
Hypercholesterolemia	53	51	55
Diabetes mellitus	11	14	7
Obesity	23	24	21
Waist–hip ratio	0.92±0.10	0.97±0.07	0.85±0.08
Physical activity			
Never	5	6	4
Exercise ≥2 d/wk	62	57	67
Higher education	46	50	42
Smoking			
Daily smoker	14	14	15
Former	46	47	44
Never	35	33	37
History of coronary heart disease	7	12	2
History of cerebrovascular event	4	5.0	2.5

Categorical variables are given as percentages, and normally distributed variables are given as mean±SD.

this population-based study. Traditional cardiovascular risk factors were common in participants with plaque and were strongly associated with increasing plaque scores.

To our knowledge, no other studies have reported such high prevalence of carotid plaques in a population of this age group. The plaque score, as a measure of plaque burden, was associated with increased prevalence of cardiovascular risk factors, as expected. In addition, plaque score was associated with a greater number of cardiovascular risk factors and with higher explained variance than cIMT, supporting the notion that atherosclerotic plaque is a more advanced stage of vascular disease. Mean cIMT was just below the 75th percentile of the proposed age- and sex-specific reference interval for common cIMT in a general population.[14] However, location, timing, and number of measurements, as well as the software algorithm, influence the cIMT results. This makes cIMT unsuitable for direct comparisons between studies and may explain higher cIMT values in our population, despite the cohort being rather healthy. Our findings reduce the value of cIMT in cardiovascular screening because almost all patients have detectable plaques.

Plaque burden increases with age.[15–17] In previous studies, the prevalence of carotid plaques has varied significantly,[3,18–24] ranging from 25% to 93%. In the present study, the definition of plaque was in accordance with the Mannheim Carotid Intima–Media Thickness and Plaque Consensus from 2004,[11] in which cIMT ≥1.5 mm was considered as a plaque, whereas earlier studies used other definitions. In addition, the studies have included either older[4,21] or younger patients,[3,5,23] men only,[21] or examination of only 1 artery.[5]

Population-based studies have shown a decrease in risk factors and cardiovascular mortality over past decades due to treatment of vascular risk in accordance with guidelines for

Table 2. Ultrasound Characteristics of the Study Population

Ultrasound Measures	Total (n=3683)	Men (n=1887)	Women (n=1796)
Mean cIMT right, mm	0.72±0.12	0.73±0.13	0.70±0.11
Mean cIMT left, mm	0.74±0.14	0.76±0.15	0.71±0.12
Plaque			
Median plaque score, IQR	2 (3)	3 (2)	2 (2)
Plaque score			
0	12.7 (11.6–13.8)	8.1 (6.9–9.4)	17.5 (15.7–19.3)
1–3	60.7 (59.2–62.4)	57.3 (55.1–59.6)	64.4 (62.2–66.6)
4–6	21.2 (19.2–62.4)	26.8 (24.6–28.9)	15.2 (13.6–16.9)
7–9	4.4 (3.7–5.1)	6.1 (5.1–7.3)	2.6 (2.0–3.6)
≥10	1.0 (0.7–1.4)	1.6 (1.1–2.3)	0.3 (0.1–0.7)
Degree of stenosis			
50–69	1.9 (1.5–2.4)	2.0 (1.4–2.7)	1.7 (1.2–2.4)
>70	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.2 (0.0–0.5)
Total occlusion	0.2 (0.1–0.4)	0.3 (0.1–0.7)	0.1 (0.0–0.3)

Categorical variables are given as percentages with 95% CI, and normally distributed variables are given as mean±SD. CI indicates confidence interval; cIMT, carotid intima–media thickness; IQR, interquartile range.

Table 3. Plaque Score in Groups in Relation to Cardiovascular Risk Factors

	Total	Percentiles						Quarters		*P* Value
		10	25	50	75	90	95	1–3	4	
Plaque score		0	1	2	4	5	7	<4	≥4	
Plaque score in groups		0	1	2	3–4	5	6–7	0–3	≥4	
Mean cIMT (mm)	0.73±0.11	0.68±0.10	0.71±0.10	0.72±0.11	0.74±0.11	0.77±0.12	0.80±0.12	0.71±0.10	0.78±0.12	<0.001
Sex (female)	48.8	67.2	58.0	52.8	40.4	33.6	28.9	54.4	33.3	<0.001
Hypertension	62.0	47.5	52.9	60.9	67.7	71.4	78.0	57.3	75.0	<0.001
Hypercholesterolemia	52.6	39.8	47.8	51.9	55.2	63.6	66.9	49.6	60.9	<0.001
Diabetes mellitus	10.4	6.6	7.7	8.8	12.7	13.3	16.7	9.0	14.2	<0.001
Obesity	22.6	20.1	21.0	21.0	24.5	25.3	26.7	21.8	25	0.047
Higher education	46.3	53.0	48.1	48.7	43.2	42.9	38.4	48.3	40.7	<0.001
Physical activity										
Never	5.0	2.4	2.5	5.4	5.2	8.5	9.6	4.1	7.5	<0.001
Exercise ≥2 d/wk	61.8	66.0	65.0	61.6	61.5	58.9	52.2	63.7	56.5	<0.001
Smoking										
Daily	14.4	6.6	7.5	12.6	15.8	24.5	33.1	10.3	25.6	<0.001
Former	45.8	44.3	44.9	44.6	48.5	46.9	44.1	45.7	46.2	0.82
Never	34.9	45.0	42.8	37.9	30.2	24.5	17.6	39.5	23.5	<0.001
History of coronary heart disease	7.1	2.4	2.2	5.2	9.4	10.8	19.8	4.7	13.7	<0.001
History of cerebrovascular event	3.8	1.7	2.3	3.4	3.9	7.5	7.9	2.9	6.2	<0.001
Score	3.6±2.4	2.8±1.5	3.3±1.8	3.7±2.2	4.2±2.7	4.6±2.8	5.1±2.9	3.5±2.1	4.8±2.9	<0.001
Low risk	0.5	1.1	1.0	0.2	0.2	0.0	0.5	0.6	0.1	0.086
Moderate risk	77.5	91.3	84.0	78.9	71.9	66.7	59.7	81.6	63.2	<0.001
High risk	19.6	7.1	14.4	18.8	24.8	28.3	33.5	16.4	31.5	<0.001
Very high risk	2.4	0.4	0.6	2.1	3.3	5.0	6.8	1.5	5.2	<0.001

Categorical variables are given as percentages, and normally distributed variables are given as mean±SD. cIMT indicates carotid intima–media thickness.

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Table 4. Poisson Regression, Plaque Score in Relation to Cardiovascular Risk Factors and Lifestyle Variables

	Univariate Exp(B)	95% CI	*P* Value	Multivariate Exp(B)	95% CI	*P* Value
Current smoking	1.741	(1.643–1.845)	<0.001	1.512	(1.436–1.591)	<0.001
Sex (female)	0.697	(0.669–0.725)	<0.001	0.743	(0.703–0.786)	<0.001
Coronary heart disease	1.667	(1.565–1.775)	<0.001	1.323	(1.237–1.237)	<0.001
Hypertension	1.386	(1.328–1.447)	<0.001	1.300	(1.243–1.359)	<0.001
Cerebrovascular disease	1.430	(1.309–1.563)	<0.001	1.254	(1.146–1.373)	<0.001
Physical inactivity	1.421	(1.198–1.556)	<0.001	1.180	(1.087–1.281)	<0.001
Hypercholesterolemia	1.251	(1.201–1.301)	<0.001	1.144	(1.096–1.195)	<0.001
Education	0.880	(0.845–0.916)	<0.001	0.947	(0.908–0.987)	0.010
Waist–hip ratio	5.559	(4.516–6.843)	<0.001	1.175	(0.863–1.599)	0.305
Obesity	1.083	(1.034–1.135)	0.001	0.979	(0.929- 1.032)	0.453
Diabetes mellitus	1.260	(1.187–1.338)	<0.001	1.009	(0.945–1.077)	0.797

Univariate and multivariate analysis. Variables with $P<0.1$ were included in the multivariate analysis. CI indicates confidence interval.

primary prevention and improved acute treatments.[25,26] The amount of atherosclerosis largely depends on the underlying burden of cardiovascular risk factors, and the increase in cardiovascular risk factor control could, in theory, have resulted in less atherosclerosis. There is no reason to believe that the ACE 1950 study population has a higher vascular burden than other population studies. This is supported by a low rate of current smoking, a mean SCORE risk of 3.6%, and a high proportion of diagnosed and treated hypertension at study inclusion. Furthermore, the low prevalence of high-grade stenosis in our study corresponds with previous studies,[4,15,16,27] suggesting a similar rather than a greater atherosclerotic burden. Despite this, our results showed the presence of plaque in 9 of 10 participants. The most reasonable explanations are the change in definition of plaque and improved ultrasonography techniques and image quality, as many previous population-based studies of B-mode ultrasound screening of carotid arteries were carried out >2 decades ago.

Despite the fact that B-mode ultrasound of the carotid arteries is effective for detecting early vascular changes, it is not used routinely in cardiovascular risk assessment. Use in clinical practice is complicated by lack of standardization regarding the definition and measurement of cIMT and its high variability, and recommended use of cIMT measurements was recently withdrawn from clinical guidelines.[28] Furthermore, a meta-analysis from 2012 concluded that the addition of cIMT measurements to the Framingham risk score was associated with a small and probably not clinically relevant improvement in risk prediction of first-time myocardial infarction or

Table 5. cIMT in Relation to Cardiovascular Risk Factors and Lifestyle Variables

	Univariate B	95% CI	*P* Value	Multivariate B	95% CI	*P* Value
Sex (female)	−0.040	(−0.048 to −0.033)	<0.001	−0.033	(−0.043–0.02)	<0.001
Hypertension	0.027	(0.019–0.034)	<0.001	0.020	(0.013–0.028)	<0.001
Obesity	0.025	(0.017–0.034)	<0.001	0.016	(0.007–0.026)	0.001
Current smoking	0.007	(0.004–0.010)	<0.001	0.013	(0.003–0.023)	0.013
Cerebrovascular disease	0.034	(0.011–0.039)	<0.001	0.023	(0.005–0.042)	0.015
Waist–hip ratio	0.198	(0.161–0.236)	<0.001	0.039	(−0.015 to 0.093)	0.154
Physical inactivity	0.016	(−0.001 to 0.033)	0.067	0.005	(−0.012 to 0.021)	0.595
Coronary heart disease	0.025	(0.011–0.039)	0.001	0.004	(−0.010 to 0.018)	0.657
Diabetes mellitus	0.020	(0.008–0.032)	0.001	0.000	(−0.012 to 0.012)	0.989
Education	−0.002	(−0.004 to 0.001)	0.171	. . .	. . .	. . .
Hypercholesterolemia	0.004	(−0.003 to 0.012)	0.256	. . .	. . .	. . .

Univariate and multivariate analysis. Variables with $P<0.1$ were included in the multivariate analysis. CI indicates confidence interval; cIMT, carotid intima–media thickness.

stroke.[29] Carotid plaque, however, compared with cIMT, has significantly higher prognostic accuracy in predicting future cardiovascular events and is recommended for risk assessment.[28,30] Increased plaque score in high-risk populations predicts coronary lesions,[31] and presence of plaque increases the risk of stroke ≈1.5-fold, independent of plaque location.[4] The same study reported a dose-dependent association between carotid plaques and stroke risk.[4] Our findings support the strong association between cardiovascular risk factors and degree of subclinical disease measured by plaque burden rather than cIMT. Consequently, we suggest that assessment of carotid plaque burden could be a useful tool in future cardiovascular screening and risk stratification, especially in populations with several risk factors, with the potential for improved risk control and primary CVD prevention.

The ultrasound procedure used in the ACE 1950 study was feasible to perform and interpret. The methodology of setting scores was easy to apply and had excellent interrater reliability. It takes only a few minutes to perform the procedure, which is suitable for use in clinical practice and as a screening tool by trained physicians, unlike measuring total plaque area, which is time consuming and probably more operator dependent. Guidelines for primary prevention include risk assessment, and measure of plaque burden may be included. Nevertheless, it remains to determined whether a higher plaque score, as a measure of plaque burden, in asymptomatic individuals is associated with an increased risk of future cardiovascular events.

Carotid plaque was more prevalent in men than in women, corresponding with other studies.[17,32] It is well documented that women in the reproductive age group are protected from developing coronary heart disease compared with men of similar age.[33] The effect is independent of cardiovascular risk factors and may be due to differences in vascular biology, including endothelial function, the production of nitric oxide,[34] and protective properties of estrogen.[33] Historically, men have had higher smoking consumption,[35] but this was not the case in the ACE 1950 cohort; however, hypertension, obesity, and diabetes mellitus were significantly more prevalent in men.

Strengths and Limitations

Self-reported information regarding lifestyle variables and medical history such as history of stroke and CVD are associated with some uncertainties. Furthermore, nonresponder bias must be taken into account; however, a response rate of 64% is considered respectable in population-based studies and is in line with other Norwegian population-based studies,[36,37] especially considering that most participants had full-time jobs and had to take a day off to participate. Furthermore, the lowest response rate was found in the municipalities located farthest away from the 2 centers. The strengths of this study are the large number of participants, trained investigators, and examination of the carotid artery on both sides. Demographically, the population is considered to represent a cross-section of the Norwegian population.

Conclusion

Carotid plaque was found in 87% of this cohort aged 63 to 65 years from the general population. Plaque burden showed greater association with traditional risk factors than cIMT. Future studies are needed to investigate the predictive ability of the plaque score for incident CVD.

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Disclosures

None.

References

1. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362:801–809.
2. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. *Curr Cardiol Rep*. 2009;11:21–27.
3. Li R, Duncan BB, Metcalf PA, Crouse JR 3rd, Sharrett AR, Tyroler HA, Barnes R, Heiss G. B-mode-detected carotid artery plaque in a general population. Atherosclerosis risk in communities (ARIC) study investigators. *Stroke*. 1994;25:2377–2383.
4. Hollander M, Bots ML, Del Sol AI, Koudstaal PJ, Witteman JC, Grobbee DE, Hofman A, Breteler MM. Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: the Rotterdam study. *Circulation*. 2002;105:2872–2877.
5. Fosse E, Johnsen SH, Stensland-Bugge E, Joakimsen O, Mathiesen EB, Arnesen E, Njolstad I. Repeated visual and computer-assisted carotid plaque characterization in a longitudinal population-based ultrasound study: the Tromso study. *Ultrasound Med Biol*. 2006;32:3–11.

6. Berge T, Vigen T, Pervez MO, Ihle-Hansen H, Lyngbakken MN, Omland T, Smith P, Steine K, Rosjo H, Tveit A. Heart and brain interactions—the Akershus Cardiac Examination (ACE) 1950 study design. *Scand cardiovasc J*. 2015;49:308–315.
7. World Health Organization. Obesity: preventing and managing the global epidemic. No. 894. World Health Organization, 2000.
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
9. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–1701.
10. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189-190.
11. Touboul P-J, Hennerici M, Meairs S, Adams H, Amarenco P, Desvarieux M, Ebrahim S, Fatar M, Kownator S, Prati P. Mannheim intima-media thickness consensus. *Cerebrovasc Dis*. 2004;18:346–349.
12. ten Kate GL, ten Kate G-JR, van den Oord SC, Dedic A, Dharampal AS, Nieman K, de Feyter PJ, Sijbrands EJ, van der Steen AF, Schinkel AF. Carotid plaque burden as a measure of subclinical coronary artery disease in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol*. 2013;111:1305–1310.
13. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI, Carroll BA, Eliasziw M, Gocke J, Hertzberg BS. Carotid artery stenosis: gray-scale and doppler us diagnosis—society of radiologists in ultrasound consensus conference 1. *Radiology*. 2003;229:340–346.
14. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, Jouven X, Empana J-P, Bozec E, Simon T, Pannier B. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J*. 2012;34:2368–2380.
15. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK, Bommer W, Price TR, Gardin JM, Savage PJ. Distribution and correlates of sonographically detected carotid artery disease in the cardiovascular health study. The CHS collaborative research group. *Stroke*. 1992;23:1752–1760.
16. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GL. Carotid artery intimal-medial thickness distribution in general populations as evaluatedbyB-modeultrasound.ARICinvestigators.*Stroke*.1993;24:1297–1304.
17. Joakimsen O, Bonaa KH, Stensland-Bugge E, Jacobsen BK. Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis: the Tromso study. *Arterioscler Thromb Vasc Biol*. 1999;19:3007–3013.
18. Coll B, Betriu A, Feinstein SB, Valdivielso JM, Zamorano JL, Fernandez E. The role of carotid ultrasound in assessing carotid atherosclerosis in individuals at low-to-intermediate cardiovascular risk. *Rev Esp Cardiol (Engl Ed)*. 2013;66:929–934.
19. Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, Lowe GD. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British regional heart study. *Stroke*. 1999;30:841–850.
20. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso study. *Stroke*. 2012;43:1818–1823.
21. Salonen R, Tervahauta M, Salonen JT, Pekkanen J, Nissinen A, Karvonen MJ. Ultrasonographic manifestations of common carotid atherosclerosis in elderly eastern finnish men. Prevalence and associations with cardiovascular diseases and risk factors. *Arterioscler Thromb*. 1994;14:1631–1640.
22. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Witteman JC, Breteler MM. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam study. *Stroke*. 2003;34:2367–2372.
23. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, Oliva B, Mocoroa A, Mendiguren J, Martinez de Vega V, Garcia L, Molina J, Sanchez-Gonzalez J, Guzman G, Alonso-Farto JC, Guallar E, Civeira F, Sillesen H, Pocock S, Ordovas JM, Sanz G, Jimenez-Borreguero LJ, Fuster V. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: The PESA (progression of early subclinical atherosclerosis) study. *Circulation*. 2015;131:2104–2113.
24. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, O'Leary DH. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. 2013;2:e000087. DOI: 10.1161/JAHA.113.000087.
25. Vangen-Lonne AM, Wilsgaard T, Johnsen SH, Lochen ML, Njolstad I, Mathiesen EB. Declining incidence of ischemic stroke: what is the impact of changing risk factors? The Tromso study 1995 to 2012. *Stroke*. 2017;48:544–550.
26. Centers for Disease Control and Prevention. Ten great public health achievements—United States, 2001–2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:619–623.
27. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, Rosvall M, Sitzer M, Buskens E, Bots ML. Prevalence of asymptomatic carotid artery stenosis in the general population an individual participant data meta-analysis. *Stroke*. 2010;41:1294–1297.
28. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol*. 2016;23:NP1–NP96.
29. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803.
30. Negi SI, Nambi V. The role of carotid intimal thickness and plaque imaging in risk stratification for coronary heart disease. *Curr Atheroscler Rep*. 2012;14:115–123.
31. Sakaguchi M, Kitagawa K, Nagai Y, Yamagami H, Kondo K, Matsushita K, Oku N, Hougaku H, Ohtsuki T, Masuyama T, Matsumoto M, Hori M. Equivalence of plaque score and intima-media thickness of carotid ultrasonography for predicting severe coronary artery lesion. *Ultrasound Med Biol*. 2003;29:367–371.
32. Zhao W, Wu Y, Shi M, Bai L, Tu J, Guo Z, Jiang R, Zhang J, Ning X, Wang J. Sex differences in prevalence of and risk factors for carotid plaque among adults: a population-based cross-sectional study in rural china. *Sci Rep*. 2016;6:38618.
33. Mathur P, Ostadal B, Romeo F, Mehta JL. Gender-related differences in atherosclerosis. *Cardiovasc Drugs Ther*. 2015;29:319–327.
34. Hayashi T, Fukuto JM, Ignarro LJ, Chaudhuri G. Gender differences in atherosclerosis: Possible role of nitric oxide. *J Cardiovasc Pharmacol*. 1995;26:792–802.
35. Ernster V, Kaufman N, Nichter M, Samet J, Yoon SY. Women and the tobacco: moving from policy to action. *Bull World Health Organ*. 2010;78:891–901.
36. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, Tverdal A, Tell GS, Nygard O, Vollset SE. The hordaland homocysteine study: a community-based study of homocysteine, its determinants, and associations with disease. *J Nutr*. 2006;136:1731s–1740s.
37. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT study, Norway. *Int J Epidemiol*. 2013;42:968–977.