Blood pressure at age 40 predicts carotid atherosclerosis two decades later: Data from the Akershus Cardiac Examination (ACE) 1950 Study

Short title: Blood pressure and atherosclerosis

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The results presented in this paper have not been presented previously.

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ABSTRACT

Objective: We assessed the impact of a single time-point measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) at the age of 40, on carotid plaque burden, echolucent plaques and carotid intima-media thickness (cIMT) late midlife.

Methods: Individuals participating in two separate studies, 23 years apart, defined our cohort (n=2714). "The Age 40 Program", a nationwide Norwegian cardiovascular screening survey, performed 1985-1999, assessed cardiovascular risk factors and lifestyle variables at age 40. "The ACE 1950 Study", a population-based cohort study on individuals born in 1950, performed 2012-2015, included ultrasound-examinations of the carotid arteries. Blood pressure determinants of carotid atherosclerosis were assessed by regression models adjusted for cardiovascular risk factors at age 40, and late midlife blood pressure.

Results: The participants, 50.3% women, had a mean age of 40 (standard deviation [SD] 0.3) years in the first study, and 64 (SD 0.6) years in the second. At age 40, mean SBP was 128 (SD 14) mmHg, mean DBP was 78 (SD 10) mmHg, and mean PP was 50 (SD 9) mmHg. SBP and DBP at age 40 predicted carotid plaque burden in late midlife. Only DBP predicted echolucent plaques, and none of the blood pressure components predicted cIMT.

Conclusion: A single time-point measurement of SBP and DBP at age 40 is associated with carotid plaque burden late midlife, also after adjustment for other cardiovascular risk factors at age 40, and of late midlife blood pressure. Our findings emphasize the strong association between blood pressure and atherosclerosis.

INTRODUCTION

Cardiovascular- and cerebrovascular diseases are leading causes of death and disability worldwide.[1] Modifiable risk factors have been postulated to explain as much as 90% of the risk of stroke and myocardial infarction,[2-4] and the increased risk of incident vascular events is reduced if preventive measures are initiated.[5] Atherosclerosis can be quantified by measurements of carotid plaque burden and carotid intima-media thickness (cIMT). Due to their ability to predict future risk of stroke and myocardial infarction, measures of carotid atherosclerosis are used as markers for subclinical disease.[6-10] Evaluation of plaque morphology is important, as echolucent plaques in particular are associated with increased risk of ischemic cerebrovascular events.[11, 12]

Among modifiable risk factors, hypertension is one of the most potent risk factor for cardiovascular disease and stroke, and the association between hypertension and stroke mortality is well established.[13, 14] Even prehypertension (120-139/80-89 mmHg) is associated with increased risk of cardiovascular events,[15, 16] and with the recent European and American guidelines for hypertension there is a clear tendency towards recommendation of stricter blood pressure treatment targets.[17, 18]

Historically, DBP was regarded the most important measure of hypertension.[19] However, with the Framingham heart study, SBP was found to be a superior predictor of cardiovascular events, especially in middle-aged and elderly people,[20] and pulse pressure (PP) is currently emerging as a strong predictor in the elderly.[21] Hypertension in elderly subjects is recognized as a principal risk factor for both carotid plaque burden and plaque progression.[22, 23] However, the impact of a single time-point measurement of blood pressure at age 40, for carotid atherosclerosis in late midlife

(age 63-65) is unknown. Accordingly, in the present study we assessed the impact of SBP, DBP and PP, at the age of 40, on carotid plaque burden, echolucent plaques and cIMT two decades later.

MATERIALS AND METHODS

Study population and data linkage

A flow chart of the study is presented in Figure 1. The Age 40 Program was a population-based national cardiovascular screening survey that aimed to assess cardiovascular risk-profiles in the young middle-aged, and was carried out between 1985 and 1999 by the National Health Screening Services. [24] All men and women in Norwegian counties were invited mainly at age 40-42 years.

The Akershus Cardiac Examination (ACE) 1950 Study is a recent and modern age cohort established to investigate the development and progression of cardiovascular and cerebrovascular disease. All men and women born in 1950 and residing in Akershus County, Norway, were invited to participate (n=5827). Examinations were performed from 2012-2015 at two study sites. In total, 3706 individuals were enrolled (participation rate 63.6%). All participants were subjected to extensive ultrasound examinations, and standardized clinical examination. The study outline and baseline results have been described previously.[25, 26]

In total, 2733 individuals participated in both the Age 40 Program and the ACE 1950 Study. In all 19 individuals were excluded; seven due to missing assessment of blood pressure in the Age 40 Program, and 12 due to missing carotid ultrasound examination

in the ACE 1950 Study, leaving 2714 subjects available for analyses in the present study.

Ethics

Informed consent was obtained from all participants. The consent also included permission to link data with previous Norwegian health examinations. The ACE 1950 Study was approved by The Regional Committees for Medical and Health Research Ethics in Norway (reference number 2011/1475), and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Cardiovascular risk factors and lifestyle variables

At inclusion in the Age 40 Program, participants filled out a questionnaire about previous or current cardiovascular- and cerebrovascular disease, diabetes mellitus, antihypertensive medications, physical activity, and smoking habits. Heart rate, SBP and DBP were measured with an automatic device (DINAMAP, Criticon, Tampa, USA). After two minutes of rest, three recordings were made at one-minute intervals, and the mean of the second and third measurement was used for analyses. Heart rate was measured simultaneously, and we chose to use the first reading as resting heart rate, since this was the lowest reading. PP was calculated as the difference between SBP and DBP. Hypertension was defined as mean SBP ≥140 mmHg, and/ or DBP ≥90 mmHg, or use of antihypertensive medication. Optimal blood pressure was defined as SBP <120 mmHg, and DBP <80mmHg, and no use of antihypertensive medication. In 116 individuals only one blood pressure measurement, without heart rate, was available and used in the analyses. Height and weight were measured, and body mass index (BMI)

calculated as body weight / height squared (kg/m^2). Total cholesterol and triglycerides were measured by an enzymatic method in non-fasting blood samples. Physical inactivity was defined as "Reading, watching television or other sedentary activity in leisure time, and less than 4 hours of low-to-moderate intensive physical activity per week". Smoking was defined as current daily smoking, and higher education was defined as a completed college or university degree (self-reported in late midlife). The study-outline of the Age 40 program has been described in detail elsewhere.[24]

In the ACE 1950 Study blood pressure was measured using an automatic monitor, Carescape V100 (GE Healthcare). After 10 minutes of rest, three readings were made at one-minute intervals, in a sitting position. Mean blood pressure was defined as the mean of the second and third reading. The use of antihypertensive and lipid-lowering agents was registered.

Carotid ultrasound

At inclusion in the ACE 1950 Study, ultrasound of both carotid arteries was performed with the ultrasound scanner Vivid E9 (GE Healthcare, Horten, Norway), equipped with a 9-MHz linear array transducer for vascular imaging. Images were digitally stored for offline analyses on custom software (Echopac, GE Vingmed).

Carotid plaque was defined according to the latest version of the Mannheim Carotid Intima-Media Thickness and Plaque Consensus, as a local thickening of the cIMT of >50% compared to the surrounding vessel wall, cIMT>1,5 mm, or a local thickening >0,5 mm, as measured from the media-adventitia interface to the intima-lumen interface.[27]

The carotid plaque score was calculated to express carotid plaque burden. The carotid

artery was assessed in four segments (common carotid artery, bifurcation, internal carotid- and external carotid artery). Plaque thickness was measured, and the segments were divided into four categories: 0, no plaque; 1,<2.5 mm; 2, 2.5-3.5 mm; and 3,>3.5 mm, based on the thickest plaque of each segment. The scores of each segment were added, giving a plaque score ranging from 0-24.[28]

Plaque morphology was registered as presence of one or more echolucent plaques. Echogenicity was evaluated by B-mode ultrasound. An echolucent plaque was defined as a dominantly low echogenic plaque, with the vessel lumen used as reference structure.[29]

cIMT was measured in B-mode and in a lateral view, with the use of a semiautomatic tracking system (Vivid E9) in the far wall of the common carotid artery. The measurements were made at least 5 mm proximal to the bulb, along 10 mm of the length in an area with identifiable double line, and in a region free from plaque. The mean values of measurements from both sides were used for analyses.

All examinations were performed by 2 physicians and 2 ultrasound technicians, trained in vascular ultrasound. The offline analyses were performed by the two physicians. We tested inter- and intrarater reliability twice during the study period. We randomly selected 25 examinations, which were analyzed with measurements of plaque diameter and plaque morphology. Both tests showed excellent results (Cronbach κ=0.999). Descriptive data from the carotid ultrasound examinations have previously been reported.[30]

Variables

In the present study, we explored SBP, DBP and PP from the Age 40 Program as main explanatory variables. Other cardiovascular risk factors and lifestyle variables were; sex, age, smoking, BMI, diabetes mellitus, antihypertensive medication, resting heart rate, total cholesterol, triglycerides, physical inactivity and higher education.

Outcome measures were carotid plaque burden, echolucent plaques and cIMT from the ACE 1950 Study. From the latter study we also used blood pressure values, and the use of antihypertensive and lipid-lowering agents.

Statistical analyses

Continuous variables are presented as means with standard deviation (SD), or medians with interquartile range. Categorical variables are presented as numbers (n) and percentages. Between-group differences were assessed using independent samples t-test for normally distributed continuous data, Mann-Whitney U test for skewed continuous data, and chi-square test for categorical data.

Poisson regression models, presented with incidence rate ratio (IRR) as effect estimate, were used to assess determinants of plaque burden, as plaque score was considered Poisson-distributed. Logistic regression models with odds ratios were used to assess determinants of echolucent plaques, and linear regression models, presented with beta coefficients (B), were used to assess determinants of cIMT (continuous variable). Logistic regression was also used to assess the determinants of plaque burden and cIMT when used as categorical variables, defined as being in the upper quartile of plaque burden, and cIMT $\geq$ 1mm.

To further elucidate the associations between carotid plaque burden and blood pressure, measures of blood pressure according to quartiles of plaque burden were assessed.

To avoid collinearity, the multivariable regression analyses were performed separately for each measure of blood pressure (Spearman's rank correlation r=0.7 between systolic and diastolic blood pressure).

For all regression analyses, univariate associations between blood pressure variables and indices of carotid atherosclerosis were presented in Model 1. The multivariable regression analyses were adjusted for sex, age, daily smoking, BMI, resting heart rate, total cholesterol, triglycerides, physical inactivity, use of antihypertensive medication, diabetes mellitus, and higher education in Model 2. In Model 3 additional adjustments were made for corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study.

Statistical significance was assumed at a two-sided p-value of <0.05. Data were analyzed using SPSS version 25 (SPSS Inc., Chicago IL).

RESULTS

Baseline characteristics from the Age 40 Program

Baseline characteristics according to sex are shown in Table 1. Mean age was 40 years, and 50% were women. Mean blood pressure was 128/78 mmHg, and mean PP was 50 mmHg. In all, 22% were defined as hypertensive, and 26% were defined as having optimal blood pressure. Men had higher blood pressure, BMI, total cholesterol, and triglycerides, but lower resting heart rate. Higher education was more prevalent among

men. The prevalence of smoking, physical inactivity, diabetes and use of antihypertensive medication was similar in men and women.

Characteristics from the ACE 1950 Study

Mean age in the ACE 1950 Study was 64 (SD 0.6) years, and median follow-up time between the two examinations was 23 (IQR 22-23) years. Median plaque score was 2, mean cIMT was 0.73 mm, and 15% had echolucent plaques (Table 1). All indices of carotid atherosclerosis were more severe in men than in women. Mean blood pressure was 138/77 mmHg, and mean PP was 61 mmHg. In all, 35% used antihypertensive medication, and 26% used lipid-lowering agents. SBP was similar in men and women. Men had significantly higher DBP, lower PP, and were more frequently using antihypertensive medication and lipid-lowering agents (Table 1).

Blood pressure at age 40 and carotid plaque burden late midlife

Blood pressure characteristics according to quartiles of plaque burden are summarized in Table 2, and presented in Figure 2. Participants in the upper quartile of plaque burden had mean blood pressure values of 132/81 mmHg, and mean PP of 51 mmHg. Moreover, 32% of the participants in the upper quartile of plaque burden were defined as hypertensive, while 18% were defined as having optimal blood pressure. In the lowest quartile of plaque burden mean blood pressure was 125/76 mmHg, and mean PP 48 mmHg. In this group, 15% of the participants were defined as hypertensive, and 33% were defined as having optimal blood pressure. All blood pressure measures, along with

number of participants defined as hypertensive, increased with increasing quartiles of plaque burden (Figure 3).

Blood pressure at age 40 as predictor of plaque burden late midlife

In univariate analyses, as well as after adjustment for cardiovascular risk factors and lifestyle variables at age 40, SBP, DBP and PP were all predictive of plaque burden (Table 3). For SBP and DBP this association remained significant also after further adjustment for corresponding blood pressure values, and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study. In the fully adjusted model, a 5 mmHg increase in SBP gave a 2.7% increase in plaque score, and for DBP a 4.6% increase was found. In contrast, the association between PP and plaque burden was attenuated and no longer significant (Table 3).

Similar associations were present when using plaque burden as a categorical variable; SBP and DBP, but not PP, predicted the upper quartile of plaque burden (Table 4).

Blood pressure at age 40 as predictor of echolucent plaques late midlife

In univariate analyses, as well as after adjustment for cardiovascular risk factors and lifestyle variables at age 40, both SBP and DBP were significantly predictive of echolucent plaques (Table 5). However, after further adjustment for corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study, only DBP remained significant. With a 5 mmHg increase in DBP, the odds of having echolucent plaques increased with 9.5% (Table 5). There was no

significant association between PP and echolucent plaques, including in univariate analysis.

Blood pressure at age 40 as predictor of cIMT late midlife

In univariate analyses, SBP, DBP and PP predicted cIMT (Supplementary Table 1). When adjusting for cardiovascular risk factors and lifestyle variables at age 40, only PP was still significantly associated with cIMT with a B-value (95% confidence interval [CI]) of 0.003 (0.000-0.005) per 5 mmHg increase. This association was attenuated and non-significant after further adjustment for corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study (Supplementary Table 1).

When dichotomizing cIMT into a categorical variable (≥1mm), the only significant association found was in univariate associations with PP (Supplementary Table 2).

DISCUSSION

In this large population based age cohort study we found that a single time-point measurement of SBP and DBP at age 40 predicted carotid plaque burden more than two decades later. DBP also predicted the presence of echolucent plaques, whereas no blood pressure components were associated with cIMT. These findings were independent of other cardiovascular risk factors and lifestyle variables at age 40, as well as corresponding blood pressure values and the use of antihypertensive and lipid-lowering

agents in the ACE 1950 Study.

To the best of our knowledge our study is the first to elucidate the associations between a single time-point measure of blood pressure in a relatively young cohort of subjects and different indices of carotid atherosclerosis two decades later.

Most population based studies performed within this field have not evaluated the relative impact of different blood pressure components (SBP, DBP and PP), and have used only one or two measures of atherosclerosis. In the Tromsø study, only SBP was considered, and found to be a predictor of both carotid plaque burden and cIMT progression.[31] In two different population-based studies SBP, but not DBP, predicted atherosclerosis and cIMT.[22, 32] SBP, DBP and PP were all examined in the PHYLLIS Study, but only SBP and PP were found to be predictors of cIMT.[33] Lastly, two independent studies, considering only SBP, found an association with echolucent plaques. [34, 35]

Moreover, the findings from these studies show that primarily SBP, PP if considered, but not DBP, predicts indices of carotid atherosclerosis. [22, 31, 32, 36, 37] These findings are supported by studies stating that systolic blood pressure is a more accurate predictor of mortality and cardiovascular complications.[20, 38]

In contrast to the above mentioned studies, we found that both SBP and DBP predicted carotid plaque burden, and only DBP predicted echolucent plaques. The reason for this might be found in the physiology of arterial aging, and the different age-range of the observed populations. Our study focused on blood pressure as a predictor in a young middle-aged population, whereas the mentioned studies included populations with a mean age of >50 years. With age, stiffening of the arteries causes the reflected pulse waves from the periphery to reach the central arteries during systole instead of diastole,

augmenting SBP, reducing DBP, and consequently increasing PP.[39, 40] As a result of this, the impact of SBP, DBP, and PP may vary depending on the age of the observed population, and SBP as well as PP may have a greater impact with increasing age.[41] In the Framingham study, association of SBP with coronary heart disease was not as pronounced in those under the age of 41. In this age group, DBP appeared to be the major predictor in men, whereas the results concerning women were inconclusive due to a very low number of participants.[20] Echolucent plaques are more vulnerable, and are more strongly associated with cardiovascular risk than predominantly echogenic plaques.[42] The detection of a potential association between blood pressure and echolucent plaques may accordingly be of great importance. Since we found only DBP to be a predictor of echolucent plaques, our results are supportive of the findings from the Framingham study, and suggestive of that DBP in early middle age should be particularly investigated when considering blood pressure treatment.

The highest proportion of individuals defined as hypertensive was found in participants with plaque burden in the upper quartile, whereas the highest proportion of individuals defined as having optimal blood pressure was found in participants in the lower quartile. Little is known about the effect of antihypertensive drugs on carotid plaques, and based on our results we cannot express an opinion concerning the effect of blood pressure treatment on subsequent carotid atherosclerosis. However, a single time-point measurement of blood pressure below 120/80 mmHg at the age of 40 is, in our study, associated with less carotid atherosclerosis two decades later.

Measurement of cIMT is the most widely used and best validated technique for imaging of atherosclerosis. The results regarding associations between blood pressure and increasing cIMT are however incongruent and conflicting, both in our and other

studies.[22, 31, 43] In our study, no measures of blood pressure predicted cIMT in the fully adjusted analyses. cIMT represents a hypertrophic adaptive response of smooth muscle cells in the tunica media to lipid infiltration or hypertension,[44] whereas carotid plaques are a later stage of atherogenesis related to inflammation, oxidation and myocyte proliferation.[45, 46] It is not fully understood why blood pressure does not seem to be a strong predictor of cIMT. In the Tromsø Study, SBP only explained 1% of subsequent increase in cIMT, and SBP was found to be negatively associated with cIMT progression.[31] The conflicting results concerning cIMT might be partly explained by difficulties concerning the validity and reliability of the cIMT measurements related to the negligible annual change in cIMT estimated at 0.01-0.04mm, which is lower than the current ultrasound pixel resolution of 0.1-0.2mm.[31, 45] The validity and reliability of the cIMT measurements have been questioned, and there is an ongoing discussion whether to measure cIMT in the common carotid artery, in an area free of plaque, or to measure cIMT in the bulb, including plaque if present.[47, 48] The first approach mainly represents hypertensive medial hypertrophy, whereas the latter approach can be considered a measure of plaque thickness and hereby a measure of atherosclerosis, possibly favoring this way of measurement in prediction of cardiovascular events.

STRENGHTS AND LIMITATIONS

Studies of age-cohorts have the advantage that the influence of age is diminished, whereas comparisons to other studies are more difficult. A great strength of the current study is the extensive systematic bilateral carotid ultrasound with examination of plaque

burden, cIMT and plaque morphology. Recall bias concerning risk factors is probably a minor problem as data was collected prospectively, and risk factors investigated were predominantly objective measurements. This study is based on measures of blood pressure at a single time-point. Considering the high variability of blood pressure, this strengthens our results in emphasizing the importance of blood pressure for later carotid atherosclerosis. However, the assignment into different blood pressure categories would have been strengthened if we had access to several measurements over a period of time. The device used to measure blood pressure was not the same in the two studies. The Dinamap used in The Age 40 Program could possibly have underestimated the real brachial blood pressure.[49] If this were the case, this would strengthen the results of our final adjusted models, where blood pressure measurements from both studies were taken into account. It would however overinflate the proportion of subjects with optimal blood pressure at The Age 40 Program, limiting external validity and consequently making it difficult to compare these results to blood pressure measured with contemporary devices. Blood pressure measures in the Age 40 Program were performed after only two minutes of rest, whereas blood pressure measures in the ACE 1950 Study were performed after 10 minutes of rest. This may attenuate the results in the final model where both blood pressure measures are taken into account. However, we believe that the associations of absolute increases in blood pressure with increasing carotid atherosclerosis remain true regardless of blood pressure devices and methods used for measurement. The fact that the participants of the current study chose to participate in two independent epidemiological studies 23 years apart, could potentially bias our results as they might be more conscious about their health.

Conclusion

A single time-point measurement of SBP and DBP at age 40 is associated with carotid atherosclerosis in late midlife, also after adjustment for cardiovascular risk factors at age 40, and of late midlife blood pressure. Our findings support the strong association between blood pressure and atherosclerosis.

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Table 1. Baseline characteristics of the study population stratified by sex.			
	Total	Female	Male	p-value
n	2714	1364 (50.3%)	1350 (49.7%)	
Age (years)	40.1 (0.3)	40.1 (0.3)	40.1 (0.3)	0.325
Weight (Kg)	73.5 (13.3)	65.2 (10.1)	81.8 (10.6)	<0.001
Height (cm)	173.0 (9.1)	166.0 (5.8)	179.5 (6.3)	<0.001
BMI (kg/m²)	24.5 (3.3)	23.6 (3.5)	25.3 (2.9)	<0.001
SBP (mmHg)	128 (14)	123 (13)	133 (12)	<0.001
DBP (mmHg)	78 (10)	76 (9)	81 (9)	<0.001
PP (mmHg)	50 (9)	47 (9)	52 (9)	<0.001
Hypertension	595 (22.0%)	165 (12.1%)	430 (31.9%)	<0.001
Optimal blood pressure	693 (25.6%)	542 (39.8%)	151 (11.2%)	<0.001
Resting heart rate (bpm)	71 (13)	74 (12)	69 (12)	<0.001
Total cholesterol (mmol/L)	5.5 (1.0)	5.2 (0.9)	5.7 (1.0)	<0.001
Triglycerides (mmol/L)	1.7 (1.3)	1.2 (0.7)	2.1 (1.5)	<0.001
Daily smoking	922 (34.0%)	478 (35.0%)	444 (32.9%)	0.236
Physical inactivity	508 (18.7%)	262 (19.2%)	246 (18.2%)	0.522
Antihypertensive medication	36 (1.3%)	13 (1.0%)	23 (1.7%)	0.087
Diabetes mellitus	7 (0.3%)	4 (0.3%)	3 (0.2%)	0.715
Higher education	1209 (44.7%)	543 (39.9%)	666 (49.5%)	<0.001
ACE 1950 Study **Indices of carotid atherosclerosis**			
Plaque score	2 (1-4)	2 (1-3)	3 (1-4)	<0.001
cIMT (mm)	0.73 (0.11)	0.71 (0.10)	0.75 (0.12)	<0.001
Echolucent plaques	410 (15.1%)	180 (13.2%)	230 (17%)	0.005
ACE 1950 Study **Blood pressure and medication**			
SBP	138 (18)	137 (19)	138 (17)	0.051
DBP	77 (10)	74 (9)	80 (10)	<0.001
PP	61 (14)	63 (15)	59 (13)	<0.001
Antihypertensive medication	949 (35.0%)	413 (30.3%)	536 (39.7%)	<0.001
Lipid-lowering agents	698 (25.7%)	300 (22.0%)	398 (29.5%)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure, PP, pulse pressure; cIMT, carotid intima-media thickness; BMI, body mass index. Variables are presented as mean (SD), median (IQR), or n (%). p-values for sex differences.

Table 2. Blood pressure and blood pressure categories according to quartiles of plaque burden.

	Q1	Q2	Q3	Q4
Plaque score	1 (0-1)	2 (2-2)	3 (3-3)	5 (4-6)
n	891	688	443	692
SBP (mmHg)	125 (13)	127 (13)*	129 (13)*	132 (15) *
DBP (mmHg)	76 (9)	78 (9) †	79 (10)*	81 (10) *
PP (mmHg)	48 (9)	49 (9) ‡	50 (9)†	51 (10) *
Hypertension	129 (14.5%)	138 (20.1%)†	108 (24.4%)*	220 (31.9%)*
Optimal blood pressure	297 (33.4%)	173 (25.2%)*	102 (23.0%)*	121 (17.5%)*

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Variables are presented as mean (SD), median (IQR), or n (%). p-values compared to Q1. *_p-value_<0.001. †_p-value_<0.01. ‡_p-value_<0.05.

	Model#1 IRR (95%CI)	Model#2 IRR (95%CI)	Model#3 IRR (95%CI)
Table 3. Blood pressure variables as predictors of plaque burden.			
SBP/5 mmHg	1.066 (1.057-1.075)*	1.046 (1.035-1.056)*	1.027 (1.016-1.038)*
DBP/5 mmHg	1.085 (1.072-1.098)*	1.059 (1.044-1.074)*	1.046 (1.030-1.063)*
PP/5 mmHg	1.054 (1.041-1.067)*	1.031 (1.017-1.045)*	1.012 (0.998-1.026)

IRR, incidence rate ratio; (95%CI), 95% confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Separate models for each blood pressure variable were computed. Model #1, unadjusted; Model #2, adjusted for sex, age, daily smoking, BMI, resting heart rate, total cholesterol, triglycerides, physical inactivity, use of antihypertensive medication, diabetes mellitus and higher education; Model #3, adjusted for Model #2, corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study. *p-value*<0.001.

	Model#1 OR (95%CI)	Model#2 OR (95%CI)	Model#3 OR (95%CI)
Table 4. Blood pressure variables as predictors of the upper quartile of plaque burden.			
SBP/5 mmHg	1.172 (1.134-1.210) *	1.126 (1.081-1.171)*	1.070 (1.025-1.117)†
DBP/5 mmHg	1.216 (1.162-1.272) *	1.164 (1.100-1.232)*	1.118 (1.051-1.190)*
PP/5 mmHg	1.140 (1.089-1.195) *	1.082 (1.025-1.141)†	1.034 (0.978-1.093)

OR, odds ratio; (95%CI), 95% confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Separate models for each blood pressure variable were computed. Model #1, unadjusted; Model #2, adjusted for sex, age, daily smoking, BMI, resting heart rate, total cholesterol, triglycerides, physical inactivity, use of antihypertensive medication, diabetes mellitus and higher education; Model #3, adjusted for Model #2, corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study. *p-value<0.001. †p-value<0.01.

	Model#1 OR (95%CI)	Model#2 OR (95%CI)	Model#3 OR (95%CI)
SBP/5 mmHg	1.068 (1.029-1.109)†	1.053 (1.005-1.102)‡	1.037 (0.986-1.090)
DBP/5 mmHg	1.093 (1.035-1.153)†	1.089 (1.021-1.163)‡	1.095 (1.020-1.176)‡
PP/5 mmHg	1.050 (0.993-1.110)	1.017 (0.955-1.082)	0.993 (0.931-1.059)

Table 5. Blood pressure variables as predictors of echolucent plaques.

OR, odds ratio; (95%CI), 95% confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Separate models for each blood pressure variable were computed. Model #1, unadjusted; Model #2, adjusted for sex, age, daily smoking, BMI, resting heart rate, total cholesterol, triglycerides, physical inactivity, use of antihypertensive medication, diabetes mellitus and higher education; Model #3, adjusted for Model #2, corresponding blood pressure values and the use of antihypertensive and lipid-lowering agents in the ACE 1950 Study. †p-value<0.01. ‡p-value<0.05

Figure 1. Flow chart of the study population.

Figure 2. Measures of blood pressure according to quartiles of plaque burden.

Figure 3. Blood pressure categories according to quartiles of plaque burden.

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