Journal of Human Hypertension (2010) 24, 86–92

www.nature.com/jhh

ORIGINAL ARTICLE

Risk factors for coronary, aortic arch and carotid calcification; The Rotterdam Study

AE Odink[1,2], A van der Lugt[2], A Hofman[1], MGM Hunink[1,2], MMB Breteler[1], GP Krestin[2] and JCM Witteman[1]

[1]*Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands and* [2]*Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands*

This study was performed to examine the association of cardiovascular risk factors with calcification in the coronary arteries, aortic arch and carotid arteries, assessed by multislice computed tomography (MSCT). This study was embedded in the Rotterdam Study, a population-based study in subjects aged 55 years and over. From October 2003 until December 2004, subjects were invited to undergo a MSCT scan. Coronary, aortic arch and carotid calcification were quantified according to the Agatston score. Analyses were performed in the first 1003 subjects. Age and current smoking were the strongest independent risk factors for arterial calcification. The odds ratio (OR) for age in women, irrespective of the vessel bed, was 1.1 ($P<0.001$) and in men it was 1.2 with aortic arch and 1.1 with carotid calcification (both $P<0.001$). Current smoking was associated with aortic arch calcification with an OR of 3.5 in women and of 4.7 in men (both $P<0.001$); and with carotid calcification with an OR of 2.1 in women ($P<0.05$) and of 4.1 in men ($P<0.01$). Hypertension, hypercholesterolemia and diabetes were also independently related to calcification, although not consistent across all vessel beds and for men and women. Obesity tended to be inversely related to arterial calcification in women, whereas low high-density lipoprotein-cholesterol showed no relation with arterial calcification. In conclusion, although associations were not completely consistent across the different vessel beds and for men and women, our results indicate that generally the same risk factors are present for atherosclerosis in the coronary, aortic arch and carotid circulation.
Journal of Human Hypertension (2010) **24,** 86–92; doi:10.1038/jhh.2009.42; published online 4 June 2009

Keywords: atherosclerosis; calcification; coronary; aortic arch; carotid; risk factors

Introduction

Atherosclerotic lesions have typical histological and histochemical compositions at different stages of their natural history.[1] More advanced atherosclerotic lesions contain calcification, although calcification may also be present in small amounts in the earlier stages of atherosclerosis.[2] Calcified lesions in the coronary arteries are correlated with the total area of coronary plaque, suggesting that calcification can be used as a measure of atherosclerosis.[3]

Several studies examined the association between cardiovascular risk factors and the presence of arterial calcification.[4–12] Until now, only one study examined associations between cardiovascular risk factors and calcification in several vessel beds, including the coronary arteries, the proximal aorta and the carotid arteries.[10] This study was performed among relatively young subjects.

We investigated the association of cardiovascular risk factors with calcification in the coronary arteries, aortic arch and the carotid arteries in a population-based study among elderly subjects.

Methods

Study population

The study is embedded in the Rotterdam Study, a population-based study, which started in 1990–1993. All inhabitants aged 55 years and older and living in a suburb of Rotterdam were invited and 7983 agreed to participate (78% response). In 2000–2001, the cohort was extended with 3011 subjects (67% response) with the same inclusion criteria. The design and rationale of the Rotterdam Study have been described elsewhere.[13] Study centre visits took place approximately every 3 years, during which cardiovascular risk factors were measured.

From September 2003 onwards, all participants who completed the centre visit (the fourth for the original cohort and the second for the extended cohort) were invited to participate in this study and to undergo a multislice computed tomography (MSCT) scan of the heart, the aortic arch and the

Correspondence: Dr JCM Witteman, Department of Epidemiology, Erasmus Medical Center, PO Box 2040, Rotterdam, 3000 CA, The Netherlands.
E-mail: j.witteman@erasmusmc.nl
Received 29 August 2008; revised 6 April 2009; accepted 11 April 2009; published online 4 June 2009

carotid arteries. We restricted the present analyses to the first 1003 participants who were scanned until December 2004. In total, 2485 subjects were scanned.

This study was approved by the Medical Ethics Committee and the Radiation Protection Unit of the Erasmus Medical Center, Rotterdam, The Netherlands. All participants gave written informed consent.

Scan protocol

In the first 708 subjects, imaging was performed with a 16-slice MSCT scanner (SOMATOM Sensation 16, Siemens, Forcheim, Germany). Two scans were performed: a cardiac scan and a scan, which included the aortic arch and the carotid arteries. The cardiac scan reached from the apex of the heart to the tracheal bifurcation. Before performing the cardiac scan, the participants exercised breath holding. Within a single breath hold consecutive non-overlapping 3-mm thick slices were acquired with 12×1.5 mm collimation, 120 kVp, effective 30 mAs, and prospective ECG triggering at 50% of the cardiac cycle. If during the exercise of the breath holding the heart rate was irregular or above 105 beats per minute, the cardiac scan was performed with 12×0.75 mm collimation, 150 effective mAs and retrospective ECG gating. For this scan, images were reconstructed at an optimal position within the cardiac cycle (defined at the position with the least motion artefacts) with 3 mm effective slice width and 1.5-mm reconstruction interval. For both cardiac scans, reconstructions were performed with 180 mm field-of-view and medium sharp convolution kernel ('B35f'). The second scan reached from the aortic arch to the intracranial circulation (1 cm above the sella turcica). Scan parameters were: 16×0.75 mm collimation, 120 kVp, 100 effective mAs, 0.5 s rotation time and normalized pitch of 1. Images were reconstructed with effective slice width 1 mm, reconstruction interval 0.5 mm, 120 mm field-of-view and medium sharp convolution kernel ('B35f'). In another 295 subjects, image acquisition was performed with a 64-slice MSCT scanner (SOMATOM Sensation 64, Siemens, Forcheim, Germany). Scan parameters were similar for both MSCT scanners, except for collimation and effective mAs. For the 64-slice MSCT scanner, the collimation was 32×0.6 mm and the mAs value was real time adapted to body weight (CARE DOSE, Siemens, Forcheim, Germany) with a reference value of 50, 190 and 100 mAs for the prospectively triggered cardiac scan, retrospectively gated cardiac scan, and the aorta-carotid scan, respectively.

Analysis of calcification

Two reviewers, with a medical background, were trained by an experienced radiologist and scored arterial calcification using a standardized protocol. They were blinded to the clinical data of the participants. Three vessel beds were analysed: the coronary arteries, the aortic arch and the carotid arteries. The examination of coronary arteries comprised the left main, left anterior descending, left circumflex and the right coronary artery. The examination of aortic arch comprised the origin of the aortic arch (defined as the image in which the ascending and descending aorta merge into the inner curvature of the aortic arch) to the first 1 cm of the common carotid arteries, the vertebral arteries and the subclavian arteries beyond the origin of the vertebral arteries. The examination of carotid arteries comprised both right and left carotid artery within 3 cm proximal and distal of the bifurcation.

Atherosclerotic calcification was identified based on a threshold of 130 Hounsfield Units, using dedicated software (syngo Calcium Scoring, Siemens, Forcheim, Germany). Calcification was quantified by calculating the Agatston score. For each calcified lesion, the Agatston score was calculated as the product of the area of a calcified lesion (the number of voxels with an attenuation value $\geqslant$130 Hounsfield Units times the volume of one voxel) and a factor assigned according to the maximum attenuation value of the lesion.[14] For image data with an overlapping reconstruction increment, Agatston scores were normalized with the ratio of increment and slice width. The total score per vessel bed was calculated by adding up the scores of all lesions.

Cardiovascular risk factors

Information on smoking, blood pressure and lipid lowering medication use was obtained during a home interview of the Rotterdam Study. Participants were asked whether they smoked, they had smoked in the past and had stopped smoking, or they had never smoked. The amount of cigarettes or cigars they smoked, or had smoked, was not registered, and the subjects were categorized as current, past and never smokers.

Clinical measurements were conducted during a visit at the study centre. Height and weight were measured, and the body mass index (BMI) was calculated (weight[kg]/height[m]^2). We defined obesity as a BMI $\geqslant 30\,kg/m^2$. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. We defined hypertension as a systolic blood pressure $\geqslant$160 mmHg and/or a diastolic blood pressure $\geqslant$100 mmHg[15] and/or the use of blood pressure lowering medication. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using an automatic enzymatic procedure (Hitachi 911, Roche CHOD PAP). We defined hypercholesterolemia as a serum total cholesterol $\geqslant 6.2\,mmol\,l^{-1}$[16] and/or the use of lipid reducing medication, low HDL-cholesterol was defined as a HDL-cholesterol $< 1.0\,mmol\,l^{-1}$.[16] Diabetes was defined as the use of anti-diabetic

medication and/or a fasting glucose level $\geqslant 7\,mmol\,l^{-1}$.[17] Information on cardiovascular disease (myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery and stroke) was collected at baseline in 1990–1993 (original cohort) or at baseline in 2000–2001 (extended cohort) and during follow-up as described earlier.[18,19] The maximum proportion of missing values of covariates was 3.2% and were handled by single imputation using an expectation-maximization algorithm.[20]

Population for analysis

In 10 subjects, the cardiac scan was not performed because of the presence of a pacemaker. Additionally, 21 subjects had a history of previous stenting in the coronary arteries. Therefore, data on coronary calcification were available for 972 subjects. Because of severe artefacts in the image acquisition, the aortic arch of one subject could not be evaluated, hence data on calcification in the aortic arch were available for 1002 subjects. Data on calcification in the carotid arteries were available for all subjects. The median duration between the study centre visit and the MSCT scan was 75 days.

Statistical analysis

We used logistic regression to determine the association between cardiovascular risk factors and arterial calcification. The highest quartile of calcification was compared with the lower three quartiles, for each vessel bed separately. As calcium scores were substantially higher in men than in women, all analyses were stratified by gender. First, the regression analysis was only adjusted for age and scanner (model 1). In model 2, additional adjustments were made for smoking status (never, current, past), obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, diabetes mellitus, history of myocardial infarction, stroke, coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty.

After exclusion of subjects with a history of cardiovascular disease, analysis of covariance was used to compute age-adjusted geometric mean calcium scores for the number of risk factors present (0, 1, 2, >2). The risk factors included (1) obesity, (2) hypertension, (3) hypercholesterolemia, (4) low HDL-cholesterol, (5) current smoking and (6) diabetes. All analyses were adjusted for the type of MSCT scanner (16 versus 64). SPSS 11.0 for Windows (SPSS, Inc, Chicago, IL, USA) was used for data analysis.

Results

Table 1 shows the characteristics of the study population. MSCT scans were obtained in 1003 subjects. The study population consisted of 48% of men. The mean age ($\pm$ s.d.) of the study participants was 72 years ($\pm$ 6.4). In total, 2485 subjects participated in this study. In the total study population, the average systolic blood pressure was lower in women ($P<0.05$) and the use of blood pressure lowering medication was lower in men ($P<0.05$).

Tables 2–4 show the age-adjusted and the multivariate adjusted odds ratios (ORs) for associations between cardiovascular risk factors and calcium scores (upper quartile versus lower three quartiles) in the different vessel beds. Age and current smoking were the strongest independent risk factors for arterial calcification. Both variables were independently associated with calcification in all vessel beds except for the coronary arteries in men. The OR for age in women, irrespective of the vessel bed, was 1.1 ($P<0.001$) and in men it was 1.2 with aortic arch and 1.1 with carotid calcification (both $P<0.001$) in the multivariate adjusted model. In the multivariate adjusted model, current smoking was associated with aortic arch calcification with an OR of 3.5 in

Table 1 Characteristics of the study population

Variable	*Men (n = 485)*	*Women (n = 518)*
Age (years)	72.0 ± 6.2	71.2 ± 6.6
Body mass index (kg/m^2)	27.2 ± 3.4	27.8 ± 4.5
Systolic blood pressure (mm Hg)	148.8 ± 20.4	150.4 ± 21.5
Diastolic blood pressure (mm Hg)	81.3 ± 11.1	79.7 ± 11.4
Total cholesterol (mmol l^{-1})	5.3 ± 0.9	5.9 ± 0.9
HDL-cholesterol (mmol l^{-1})	1.3 ± 0.3	1.5 ± 0.4
Fasting glucose (mmol l^{-1})	5.8 ± 1.3	5.7 ± 1.3
Diabetes mellitus (%)	12	10
Smokers (%)		
Current	13	15
Past	73	43
Never	14	42
Use of blood pressure lowering medication (%)	45	48
Use of lipid lowering medication (%)	26	23
History of myocardial infarction (%)	12	5
History of stroke (%)	5	4
Coronary artery bypass graft (%)	6	1
Percutaneous transluminal coronary	3	1
Angioplasty (%)		
Coronary artery Agatston score[a]	207.3 (32.6–728.8)	33.7 (0.2–189.2)
Aortic arch Agatston score[a]	513.6 (83.4–1607.7)	370.9 (78.7–1245.4)
Carotid artery Agatston score[a]	64.1 (2–234.8)	25.7 (0–128.6)

Categorical variables are expressed as percentage. Values of continuous variables are expressed as mean ± s.d.
[a]Value is expressed as median (interquartile range) because of its skewed distribution.

Table 2 Relation between putative risk factors and presence of severe calcification in the coronary arteries (upper quartiles versus lower three)

Variable	*(Exposed (%))*	*Model 1*	*Model 2*
		OR (95% CI)	*OR (95% CI)*
Men			
Age (years)		1.1 (1.0–1.1)[b]	1.0 (1.0–1.1)
BMI $\geqslant$ 30 kg/m^2	92 (20)	1.4 (0.8–2.3)	1.0 (0.5–1.8)
Hypertension	263 (57)	2.1 (1.3–3.4)[b]	1.6 (1.0–2.7)
Hypercholesterolemia	191 (41)	2.6 (1.7–4.1)[a]	1.9 (1.2–3.1)[b]
HDL $<$ 1.0 mmol l^{-1}	67 (14)	0.8 (0.4–1.5)	0.7 (0.4–1.4)
Current smoking	59 (13)	1.1 (0.4–2.5)	1.2 (0.5–3.1)
Past smoking	337 (72)	1.3 (0.7–2.5)	1.1 (0.6–2.3)
Diabetes	57 (12)	2.5 (1.4–4.4)[b]	1.9 (1.0–3.6)[c]
Women			
Age (years)		1.1 (1.1–1.1)[a]	1.1 (1.0–1.1)[a]
BMI $\geqslant$ 30 kg/m^2	131 (26)	1.1 (0.7–1.7)	0.8 (0.4–1.3)
Hypertension	268 (53)	2.6 (1.6–4.1)[a]	2.3 (1.4–3.7)[a]
Hypercholesterolemia	276 (54)	1.7 (1.1–2.6)[c]	1.5 (1.0–2.3)
HDL $<$ 1.0 mmol l^{-1}	34 (7)	1.3 (0.6–2.8)	0.8 (0.3–2.0)
Current smoking	76 (15)	2.0 (1.1–3.6)[c]	1.8 (1.0–3.6)
Past smoking	212 (42)	1.2 (0.8–1.9)	1.3 (0.8–2.0)
Diabetes	52 (10)	2.0 (1.1–3.7)[b]	2.0 (1.0–4.0)[c]

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein.
Model 1: adjusted for age and scanner.
Model 2: additionally adjusted for smoking status (never, current, past), obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, diabetes mellitus, history of myocardial infarction, stroke, CABG and PTCA.
[a]$P<0.001$.
[b]$0.001<P<0.01$.
[c]$0.01<P<0.05$.

Table 3 Relation between putative risk factors and presence of severe calcification in the aortic arch (upper quartiles versus lower three)

Variable	*(Exposed (%))*	*Model 1*	*Model 2*
		OR (95% CI)	*OR (95% CI)*
Men			
Age (years)		1.1 (1.1–1.2)[a]	1.2 (1.1–1.2)[a]
BMI $\geqslant$ 30 kg/m^2	97 (20)	2.6 (1.5–4.5)[a]	2.5 (1.4–4.6)[c]
Hypertension	273 (56)	2.5 (1.5–4.1)[a]	2.1 (1.2–3.5)[b]
Hypercholesterolemia	208 (43)	2.4 (1.5–3.8)[a]	1.6 (1.0–2.7)
HDL $<$ 1.0	70 (14)	0.8 (0.4–1.5)	0.6 (0.3–1.1)
Current smoking	59 (12)	3.2 (1.3–7.9)[c]	4.7 (1.8–12.6)[a]
Past smoking	354 (73)	1.6 (0.8–3.3)	1.4 (0.6–3.1)
Diabetes	58 (12)	1.2 (0.6–2.3)	0.8 (0.4–1.6)
Women			
Age (years)		1.1 (1.1–1.2)[a]	1.1 (1.1–1.2)[a]
BMI $\geqslant$ 30 kg/m^2	134 (26)	0.8 (0.5–1.2)	0.6 (0.4–1.1)
Hypertension	277 (53)	1.4 (0.9–2.3)	1.4 (0.8–2.2)
Hypercholesterolemia	286 (55)	1.2 (0.8–1.8)	1.0 (0.6–1.5)
HDL $<$ 1.0	34 (7)	1.3 (0.6–2.9)	0.9 (0.4–2.4)
Current smoking	81 (16)	3.8 (2.0–7.1)[a]	3.5 (1.8–6.8)[a]
Past smoking	224 (43)	1.6 (1.0–2.7)	1.7 (1.0–2.8)[c]
Diabetes	53 (10)	1.8 (1.0–3.4)	2.2 (1.3–4.9)[c]

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein.
Model 1: adjusted for age and scanner.
Model 2: additionally adjusted for smoking status (never, current, past), obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, diabetes mellitus, history of myocardial infarction, stroke, CABG and PTCA.
[a]$P<0.001$.
[b]$0.001<P<0.01$.
[c]$0.01<P<0.05$.

women and of 4.7 in men (both $P<0.001$; and with carotid calcification with an OR of 2.1 in women ($P<0.05$) and of 4.1 in men ($P<0.01$). Past smoking was only associated with arterial calcification in women in the aortic arch, and in men in the carotid arteries. Hypertension, hypercholesterolemia and diabetes were significant or near significant risk factors for arterial calcification except for hypertension in women in the aortic arch and men in the carotid arteries, hypercholesterolemia for women in the aortic arch, and diabetes for men in the aortic arch and carotid arteries.

In men, obesity was not related to calcification in the coronary arteries and carotid arteries, but a significant independent association was found with aortic arch calcification. In women, obesity tended to be inversely related to arterial calcification, which was significant for carotid calcification. Low HDL-cholesterol was not associated with arterial calcification in any of the vessel beds.

Table 5 shows the prevalence of calcification in the different vessel beds, categorized by gender and for the complete study population. In 2.9% of the study population, no calcification was found. However, in over 60%, the subjects had arterial calcification in the three beds.

Figure 1 shows the geometric mean calcium score according to the number of risk factors in asymptomatic subjects. In both men and women, the number of risk factors was strongly associated with the calcium score for all vessel beds. Compared with subjects without risk factors, calcium scores in all three vessel beds were significantly elevated in subjects with 2 or more than 2 risk factors, except for calcium scores in the aortic arch in men with more than 2 risk factors. In women with 1 risk factor, calcium scores in the aortic arch and in the carotid arteries were significantly elevated compared with women without risk factors.

Discussion

In this study, we examined the relation between cardiovascular risk factors and coronary, aortic arch and carotid calcification. Our results showed that current smoking, hypertension, hypercholesterolemia and diabetes were independently related to arterial calcification, although associations were not consistent across all vessel beds and for men and women. A tendency was present for an inverse association with obesity in women, whereas no

Table 4 Relation between putative risk factors and presence of severe calcification in the carotid arteries (upper quartiles versus lower three)

Variable	*(Exposed (%))*	*Model 1*	*Model 2*
		OR (95% CI)	*OR (95% CI)*
Men			
Age (years)		1.1 (1.1–1.1)[a]	1.1 (1.1–1.2)[a]
BMI $\geqslant$ 30 kg/m^2	97 (20)	1.5 (0.9–2.6)	1.3 (0.8–2.4)
Hypertension	274 (56)	1.3 (0.8–2.0)	1.0 (0.6–1.7)
Hypercholesterolemia	209 (43)	1.9 (1.2–3.0)[b]	1.4 (0.9–2.3)
HDL $<$ 1.0	70 (14)	0.9 (0.5–1.6)	0.8 (0.4–1.5)
Current smoking	59 (12)	3.6 (1.3–8.9)[b]	4.1 (1.5–10.8)[b]
Past smoking	355 (73)	2.6 (1.2–5.8)[c]	2.4 (1.1–5.4)[c]
Diabetes	58 (12)	1.5 (0.8–2.8)	1.2 (0.6–2.4)
Women			
Age (years)		1.1 (1.1–1.1)[a]	1.1 (1.1–1.1)[a]
BMI $\geqslant$ 30 kg/m^2	134 (26)	0.7 (0.4–1.1)	0.5 (0.3–0.9)[b]
Hypertension	277 (53)	2.2 (1.4–3.5)[a]	2.0 (1.2–3.3)[c]
Hypercholesterolemia	286 (55)	2.8 (1.8–4.4)[a]	2.5 (1.6–4.1)[a]
HDL $<$ 1.0	34 (7)	1.8 (0.8–3.8)	1.4 (0.6–3.4)
Current smoking	81 (16)	2.6 (1.4–4.7)[a]	2.1 (1.1–4.1)[c]
Past smoking	224 (43)	1.1 (0.7–1.8)	1.1 (0.7–1.9)
Diabetes	53 (10)	1.8 (1.0–3.4)	2.1 (1.0–4.1)[c]

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein.
Model 1: adjusted for age and scanner.
Model 2: additionally adjusted for smoking status (never, current, past), obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, diabetes mellitus, history of myocardial infarction, stroke, CABG and PTCA.
[a]$P<0.001$.
[b]$0.001<P<0.01$.
[c]$0.01<P<0.05$.

Table 5 Prevalence of calcification in the different vessel beds, categorized by gender

Vessel	*Men % (n = 485)*	*Women % (n = 518)*	*Total (%) (n = 1003)*
No calcification	2.7	3.1	2.9
Coronary arteries*	1.9	1.9	1.9
Aortic arch*	2.3	6.9	4.7
Carotid arteries*	0.6	1.4	1.0
Coronary arteries and aortic arch*	14.6	15.6	15.2
Coronary and carotid arteries*	4.1	2.1	3.1
Aortic arch and carotid arteries*	6.4	14.3	10.5
Coronary arteries, aortic arch and carotid arteries*	67.4	54.6	60.8

*Calcification in the mentioned vessels.

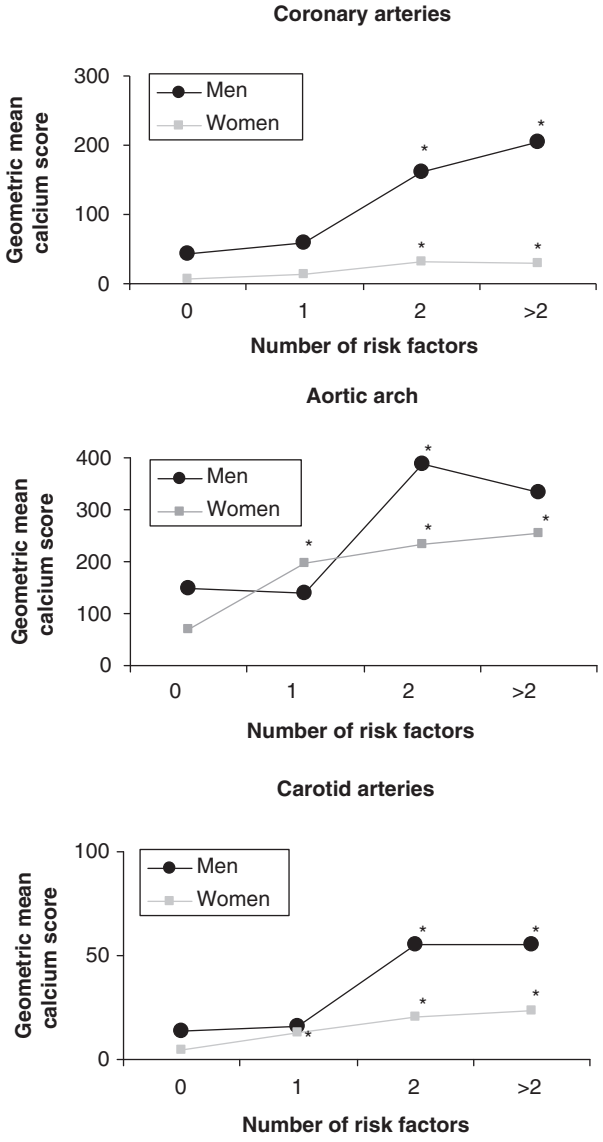

Figure 1 Geometric mean calcium score according to the number of risk factors. *$P<0.05$ with no risk factors as the reference category.

association with low HDL-cholesterol and arterial calcification was present.

Associations between cardiovascular risk factors and arterial calcification have been studied before.[4–12] The study population was relatively young in most studies, except for two of the studies.[5,7] Most of these studies investigated the association between cardiovascular risk factors and the presence of calcification in one vessel bed only.[4,5,7–9,11] In postmenopausal women[12] and in asymptomatic patients who were self- or physician-referred,[6] the association of cardiovascular risk factors with coronary and aortic calcification was examined. In one study,[10] among subjects who were self- or physician-referred, cardiovascular risk factors were related to coronary, aortic, carotid and iliac calcification. The study population of this study consisted of 650 subjects with an average age of 57.6 years. To our knowledge, our study is the first that examined the association of cardiovascular risk factors with coronary, aortic arch and carotid calcification in a non-selected population of elderly subjects.

In this study, we found that age and current smoking were the strongest risk factors for arterial calcification in all vessel beds, except for coronary calcification in men. Possibly men who smoke are prone to die from coronary heart disease at an earlier age due to selective mortality. Other studies show

independent associations of smoking with coronary, aortic arch and carotid calcification in generally younger populations[4,5,7–9,11]

Hypertension, hypercholesterolemia and diabetes were independent risk factors, although associations were not consistent across all vessel beds and for men and women. Other studies found independent associations between blood pressure variables and coronary calcification[4,8,10,11] aortic arch calcification[11] and carotid calcification.[10] A study by Hoff *et al*.[4] among 30 908 asymptomatic individuals showed an independent association of hypercholesterolemia with coronary calcification in both men and women. A study among family members of cardiac patients[9] found an independent association between statin use and coronary calcification in both genders and an independent association between total cholesterol and coronary calcification in women. Iribarren *et al*.[11] found an independent association between serum cholesterol above 6.6 mmol/l and aortic arch calcification only in women. A study by Allison *et al*.[10] examining risk factors for coronary, proximal aorta and carotid calcification, found age-adjusted associations in both genders between hypercholesterolemia and arterial calcification in all vessels, except for coronary calcification in men, but all the associations lost significance after multivariate adjustment. In summary, relations between cholesterol and calcification in studies were not consistent across vessel beds and across men and women, but generally the association was present.

Data on diabetes and its relation to arterial calcification are inconsistent. A study by Hoff *et al*.[4] showed an association of diabetes with coronary calcification in both men and women, Reilly *et al*.[9] found an association between fasting glucose and coronary calcification in women only, whereas no association of fasting glucose with both coronary and aortic calcification was found in a study among postmenopausal women.[12] Iribarren *et al*.[11] did not find an association between diabetes and aortic arch calcification in both men and women. Allison *et al*.[10] examined the association between diabetes and calcification in several arteries, and only found a univariate association with calcification in the proximal aorta in men.

Obesity in men was not related to arterial calcification, except for aortic arch calcification. In women, a tendency was found for an inverse association; however, this was only significant for carotid calcification. An inverse association in women, but not in men may be related to estrogen production in fat mass in women after menopause.[21] Results from the literature regarding the association between obesity and calcification are inconsistent. Irrespective of gender, some studies found an association of BMI with coronary calcification[9,10] and one study found a high BMI to be inversely associated with aortic calcification.[11] However, other studies found no association with coronary calcification,[8] aortic calcification[10] and carotid calcification[10] in both genders.

We found no clear association of low HDL with calcification for all vessel beds. It is possible that this is due to small numbers because only a small percentage of our subjects had a low HDL-cholesterol. Data on the relation between HDL-cholesterol and arterial calcification are not only scarce but also contradictory. Reilly *et al*.,[9] in a study among family members of cardiac patients, found an age-adjusted association of low HDL with coronary calcification in both men and women, Oei *et al*.[5] found an independent association with coronary calcification only in women, whereas Allison and Wright[8] found an independent relation between HDL-cholesterol and coronary calcification in men and women. In a study by Kuller *et al*.,[12] an independent association of HDL-cholesterol with coronary calcification but not with aortic calcification was observed.

We have investigated the association between cardiovascular risk factors and arterial calcification. We used arterial calcification as a proxy for atherosclerosis. Overall, our results indicate that generally the same risk factors are present for atherosclerosis in the coronary, aortic arch and carotid circulation. However, except for coronary artery calcification,[22–24] the prognostic value of arterial calcification for cardiovascular events is unknown. The predictive value of arterial calcification in the aortic arch and the carotid arteries needs to be examined in future research, preferably in a prospective study design.

The advantages of our study are its large population and the inclusion of three vessel beds measured by the same diagnostic tool. As calcification was measured without knowledge of risk factor status, information bias is not likely to have influenced our results. However, some limitations of our study need to be discussed. In our study, we measured calcification, not plaque *per se*. Although calcification is not a direct measure of plaque, coronary calcification determined by electron beam computed tomography has been correlated with the total area of coronary plaque.[3] Also, the presence of aortic calcification on chest radiographs has been shown to indicate aortic atherosclerosis.[25] To the best of our knowledge, there are no data on the relation between carotid artery calcification and carotid plaque burden. As long as we do not have reasons to assume that the process of calcification differs across vessel beds, we believe that carotid artery calcification reflects carotid atherosclerosis. Our study may be further limited by the fact that non-participation of diseased subjects may have resulted in a relatively healthy study population, with a more restricted range of calcium scores, which may lead to an underestimation of the associations. Finally, our cutoff points for high calcification depend on the distribution of calcification per vessel bed and gender and may be different in other populations.

What is known about the topic:
Arterial calcification:
- Occurs in a more advanced atherosclerotic lesion
- In the coronary arteries can be used as a measure for atherosclerosis

What this study adds:
- Our study is the first large population-based study that examined the association of cardiovascular risk factors and arterial calcification in several vessel beds
- Our study indicates that, generally, the same cardiovascular risk factors are present for atherosclerosis in the coronary, aortic arch and carotid circulation

Acknowledgements

This study was supported by grants from the Netherlands Heart Foundation (2003B179) and the Netherlands Organization for Scientific Research (NWO, 015.000.090). We thank all participants of the Rotterdam study for their contributions.

References

1 Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull Jr W *et al.* A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol* 1995; **15**: 1512–1531.
2 Stary HC. The sequence of cell and matrix changes in atherosclerotic lesions of coronary arteries in the first forty years of life. *Eur Heart J* 1990; **11**: 3–19.
3 Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995; **92**: 2157–2162.
4 Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukov A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30 908 healthy individuals. *Ann Epidemiol* 2003; **13**: 163–169.
5 Oei HH, Vliegenthart R, Hofman A, Oudkerk M, Witteman JC. Risk factors for coronary calcification in older subjects. The Rotterdam Coronary Calcification Study. *Eur Heart J* 2004; **25**: 48–55.
6 Wong ND, Sciammarella M, Arad Y, Miranda-Peats R, Polk D, Hachamovich R *et al.* Relation of thoracic aortic and aortic valve calcium to coronary artery calcium and risk assessment. *Am J Cardiol* 2003; **92**: 951–955.
7 Newman AB, Naydeck BL, Sutton-Tyrrell K, Feldman A, Edmundowicz D, Kuller LH. Coronary artery calcification in older adults to age 99: prevalence and risk factors. *Circulation* 2001; **104**: 2679–2684.
8 Allison MA, Wright CM. Age and gender are the strongest clinical correlates of prevalent coronary calcification (R1). *Int J Cardiol* 2005; **98**: 325–330.
9 Reilly MP, Wolfe ML, Localio AR, Rader DJ. Coronary artery calcification and cardiovascular risk factors: impact of the analytic approach. *Atherosclerosis* 2004; **173**: 69–78.
10 Allison MA, Criqui MH, Wright CM. Patterns and risk factors for systemic calcified atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004; **24**: 331–336.
11 Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *JAMA* 2000; **283**: 2810–2815.
12 Kuller LH, Matthews KA, Sutton-Tyrrell K, Edmundowicz D, Bunker CH. Coronary and aortic calcification among women 8 years after menopause and their premenopausal risk factors: the healthy women study. *Arterioscler Thromb Vasc Biol* 1999; **19**: 2189–2198.
13 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991; **7**: 403–422.
14 Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte Jr M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15**: 827–832.
15 Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
16 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.
17 American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005; **28**: S4–S36.
18 Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* 2003; **74**: 317–321.
19 van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation* 2004; **109**: 1089–1094.
20 Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. *J Roy Stat Soc* 1977; **Ser B**: 1–39.
21 Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C *et al.* Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst* 2003; **95**: 1218–1226.
22 Newman AB, Naydeck BL, Ives DG, Boudreau RM, Sutton-Tyrrell K, O'Leary DH *et al.* Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. *Am J Cardiol* 2008; **101**: 186–192.
23 Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijck W, van Rooij FJ *et al.* Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005; **112**: 572–577.
24 Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA *et al.* Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 2008; **168**: 1333–1339.
25 Hyman JB, Epstein FH. A study of the correlation between roentgenographic and post-mortem calcification of the aorta. *Am Heart J* 1954; **48**: 540–543.