



Gender and age effects on risk factor-based prediction of coronary artery calcium in symptomatic patients: A Euro-CCAD study

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ABSTRACT

Background and aims: The influence of gender and age on risk factor prediction of coronary artery calcification (CAC) in symptomatic patients is unclear.

Methods: From the European Calcific Coronary Artery Disease (EURO-CCAD) cohort, we retrospectively investigated 6309 symptomatic patients, 62% male, from Denmark, France, Germany, Italy, Spain and USA. All of them underwent risk factor assessment and CT scanning for CAC scoring.

Results: The prevalence of CAC among females was lower than among males in all age groups. Using multivariate logistic regression, age, dyslipidaemia, hypertension, diabetes and smoking were independently predictive of CAC presence in both genders. In addition to a progressive increase in CAC with age, the most important predictors of CAC presence were dyslipidaemia and diabetes ($\beta = 0.64$ and 0.63 , respectively) in males and diabetes ($\beta = 1.08$) followed by smoking ($\beta = 0.68$) in females; these same risk factors were also important in predicting increasing CAC scores. There was no difference in the predictive ability of diabetes, hypertension and dyslipidaemia in either gender for CAC presence in patients aged <50 and 50–70 years. However, in patients aged >70, only dyslipidaemia predicted CAC presence in males and only smoking and diabetes were predictive in females.

Conclusions: In symptomatic patients, there are significant differences in the ability of conventional risk factors to predict CAC presence between genders and between patients aged <70 and ≥ 70 , indicating the important role of age in predicting CAC presence.

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1. Introduction

Coronary artery calcification (CAC) is calcium formation in one or more of the layers of the coronary wall. It is an independent predictor of cardiovascular (CV) events and all-cause mortality in

both CV and renal patients [1,2] and is thought to be a manifestation of sub-clinical atherosclerosis in asymptomatic individuals [3]. Significant CAC can cause diffuse hardening of the arteries, which may result in exertional angina even in the absence of significant flow limiting lesions [4]. Since treatment of atherosclerosis by statins fails to attenuate CAC progression [5], it might be helpful to determine the potential relationship of CAC with other conventional CV risk factors, with the hope that their treatment might reduce CAC formation.

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The conventional CV risk factors (dyslipidaemia, hypertension, diabetes mellitus, family history of coronary artery disease (CAD), obesity and smoking) have proved useful in quantifying the estimated 10-year coronary event risk [6] but their relationship with CAC presence has not been fully determined in symptomatic patients. The European Calcific Coronary Artery Disease (EURO-CCAD) study, an international platform established in 2009 in Umeå, Sweden, was initiated with the objective of increasing knowledge of the relationship between coronary calcium and conventional as well as other risk factors. This retrospective cross-sectional study investigates the influence of gender and age on the relationship between conventional CV risk factors and CAC presence in 6309 symptomatic patients.

2. Patients and methods

Retrospective data were collected from seven heart centres in six countries, on symptomatic patients with intermediate (10–20%) 10-year risk for developing coronary heart disease [7]. Some data were collected from registries. Patients may have typical or atypical angina symptoms; data allowing classification of chest pain as typical angina, atypical angina or non-cardiac chest pain as defined by Diamond [8] were not available although it was estimated that the majority had typical angina. Patients received a thorough clinical examination and assessment of conventional risk factors for CAD, together with coronary calcium scoring using the local CT protocol.

These patients were collected from the following centres:

Denmark: 1015 patients from 2 centres
 France: 547 patients
 Germany: 351 patients
 Italy: 3336 patients
 Spain: 186 patients
 USA: 874 patients.

The exclusion criteria for this study were:

- acute coronary syndrome or recent cardiovascular event
- stroke or transient ischaemic attack
- cardiac valve disease
- atrial fibrillation
- prior coronary intervention (percutaneous intervention or bypass graft surgery)
- heart failure or previous decompensation
- chronic kidney disease (creatinine >120 mmol/l)
- parathyroid disease
- pregnancy.

2.1. Computed tomography scanning protocol

CT scanning for coronary calcification was undertaken with the patient in the supine position. The heart was localized by low-dose, low-resolution spiral CT imaging of the chest. High-resolution scanning of the heart was begun at the level of the bifurcation of the main pulmonary artery and proceeded caudally through the cardiac apex. Rotation and slice acquisition protocols were adopted according to individual scanners and local protocols. At least four contiguous pixels with a CT density ≥ 130 Hounsfield units were used to define an area of CAC. The total CAC score (CACS) was computed from all calcified lesions by means of the Agatston score, calculated by multiplying the area of each lesion by a density factor and then summing the individual lesion scores [9]. Analyses were performed using local protocols and workstations [10].

2.2. Risk factor assessment

All centres used standard definitions for risk factors. Diabetes was defined as overnight fasting blood glucose ≥ 7 mmol/l (126 mg/dl), postprandial blood glucose ≥ 11 mmol/l (200 mg/dl) or use of insulin or oral hypoglycemic agents. Blood lipids were measured using standard enzymatic methods. Hypercholesterolaemia was defined as total cholesterol >5.0 mmol/l (193 mg/dl), low density lipoprotein cholesterol >3.00 mmol/l (116 mg/dl) or use of lipid-lowering medication. Body mass index (BMI) was calculated using height and weight measurements, with BMI ≥ 30 kg/m² indicating obesity. Family history of premature CAD was noted if a male first-degree relative developed CAD aged <55 years or a female first-degree relative aged <65 years. Hypertension was defined according to the JNC-7 guidelines as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive medication [11]. Patient was classified as smokers if they had smoked during the last month. A total risk factors score was created by counting 1 for each risk factor present, with the exception of age.

2.3. Statistical analysis

Statistical analysis was undertaken using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ SD or median, and differences between groups were analysed by Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables were expressed as absolute value and percentage and differences were analysed by Chi-square test. Covariates-adjusted odds ratios (OR) and 95% confidence intervals (CI) of risk factors were derived from the Multivariate Logistic Regression models. To assess the stability of the derived models, 10-fold cross-validation was used, where the corresponding classification accuracy, sensitivity and specificity were determined for each of the ten models. Classification results based on different sets of explanatory variables were compared using nonparametric methods. A *p*-value of <0.05 was considered statistically significant. For obesity, approximately 40% of values were missing and consequently obesity was analysed separately. Patients with missing values were excluded from the Multivariate Logistic Regression analysis.

3. Results

3.1. Comparison of prevalence of risk factors between males and females, with and without CAC

Table 1 shows the distribution of risk factors according to gender in 6309 symptomatic patients classified by whether or not they had any CAC. This analysis shows that irrespective of the presence or absence of CAC, females recruited into this study were older than males by approximately 5 years. The mean age of males with CAC was 62 years, compared to those with zero CAC whose mean age was 51 years, whereas in females the mean age of those with CAC was 66 years, with a mean age of 57 years in those with zero CAC. Regardless of CAC presence, females more frequently had hypertension and a family history of CAD, whereas males were more frequently smokers and had a higher number of risk factors. In patients with zero CAC, females more frequently had dyslipidaemia. There was no difference between males and females for incidence of diabetes or obesity, irrespective of CAC presence, and in patients with CAC there was no difference in the incidence of dyslipidaemia between genders.

Table 2 shows the distribution of the proportion of males and females with and without CAC in different age groups. This shows

Table 1

Comparison of prevalence of risk factors between males and females and between patients with and without CAC.

Risk factors	CAC = 0 (n = 2132)			CAC>0 (n = 4177)		
	Female n = 1130	Male n = 1002	p-value	Female n = 1268	Male n = 2909	p-value
Age, years, mean $\pm$ SD	57.1 $\pm$ 11.2	51.1 $\pm$ 10.7	<0.001	66.3 $\pm$ 10.1	62.0 $\pm$ 10.6	<0.001
Family history of CAD, yes/total, %	565/1112 (57.9)	417/990 (42.1)	<0.001	589/1219 (48.3)	1181/2763 (42.7)	0.001
Smoking, yes/total, %	301/1120 (26.9)	376/998 (37.7)	<0.001	378/1255 (30.1)	1041/2895 (36.0)	<0.001
Diabetes mellitus, yes/total %	81/1124 (7.2)	71/999 (7.1)	0.99	232/1254 (18.5)	492/2901 (17.0)	0.23
Hypertension, yes/total %	549/1125 (48.8)	387/998 (38.8)	<0.001	835/1263 (66.1)	1808/2901 (62.3)	0.02
Dyslipidaemia, yes/total, %	433/1074 (40.3)	323/967 (33.4)	0.001	653/1258 (53.3)	1455/2830 (51.4)	0.45
Obesity, yes/total, %	102/631 (16.2)	118/638 (18.5)	0.30	140/699 (20.0)	394/1712 (23.0)	0.12
Number of risk factors, mean $\pm$ SD	1.83 $\pm$ 1.15	2.09 $\pm$ 1.29	<0.001	2.37 $\pm$ 1.19	2.82 $\pm$ 1.36	<0.001

CAC, CAC score; CAD, coronary artery disease.

Table 2

Proportion of patients with and without CAC by gender in different age groups.

10-year age group	Males		Females		p-value
	CAC = 0 n = 1002	CAC>0 n = 2909	CAC = 0 n = 1130	CAC>0 n = 1268	
30–39 yr	70.8% (170)	29.1% (70)	86.1 (87)	13.9 (14)	0.003
40–49 yr	48.5 (336)	51.5 (357)	76.2 (234)	23.8 (73)	<0.001
50–59 yr	25.7 (290)	74.3 (840)	56.9 (359)	43.3 (273)	<0.001
60–69 yr	14.3 (165)	85.7 (991)	42.3 (321)	57.7 (437)	<0.001
≥ 70 yr	5.9 (41)	94.1 (651)	21.5 (129)	78.5 (471)	<0.001

CAC, CAC score; numbers are % (n), where percentages in each age range indicate the % of the number of that gender with or without CAC in the respective age-group.

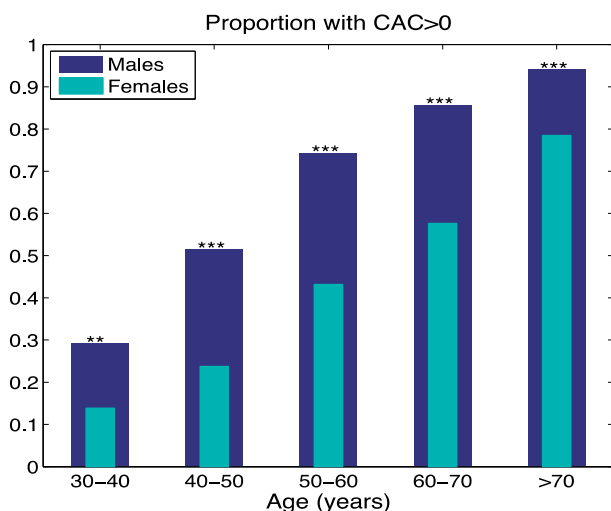
that in males, among those aged 30–39 years there are more subjects without than with CAC, while at age 40–49 years proportions are similar, and at older age, proportions with CAC exceeded those without and increased with age. Among females, the proportion of subjects without CAC exceed that of subjects with CAC up to approximately age 60 years, when the proportion of those with CAC exceed those without and increase with age. Similarly, Fig. 1 shows that the proportion of patients with CAC is

significantly higher for males in all age groups, compared to females, and that there is a linear increase in the proportion of both genders with CAC with increasing age.

Fig. 2 demonstrates that in both males and females, the mean number of risk factors was 2, with both distributions showing a similar pattern, an approximate normal distribution. Fig. 3 shows the proportion of patients with CAC in different age groups by gender, according to the presence or absence of the four modifiable risk factors (smoking, diabetes mellitus, hypertension, dyslipidaemia). This demonstrates a fairly linear increase in both genders with increasing age, indicating that in each age group the proportion with at least one modifiable risk factor always exceeds those with no risk factors, which seems to be more marked among females. Fig. 4 shows boxplots comparing the number of risk factors against an increasing CAC score in males and females. This analysis demonstrates that, in both males and females, the median and interquartile CAC scores increase with the number of risk factors, possibly more dramatically in females than males, but, as expected, are always lower in females than males except among females with ≥ 4 risk factors, when CAC extent approaches that of males. This figure also demonstrates that it is possible to have relatively high CAC but no risk factors in both genders.

3.2. Univariate risk factor prediction of CAC presence

Table 3 shows the univariate regression analysis to identify risk factors predictive of a CAC score >0 , ≥ 100 , ≥ 400 and ≥ 1000 compared to zero CAC, divided by gender and corrected for age. This table shows that in males, family history of CAD, smoking, diabetes,

**Fig. 1.** Proportion of patients with CAC by gender in different age groups.

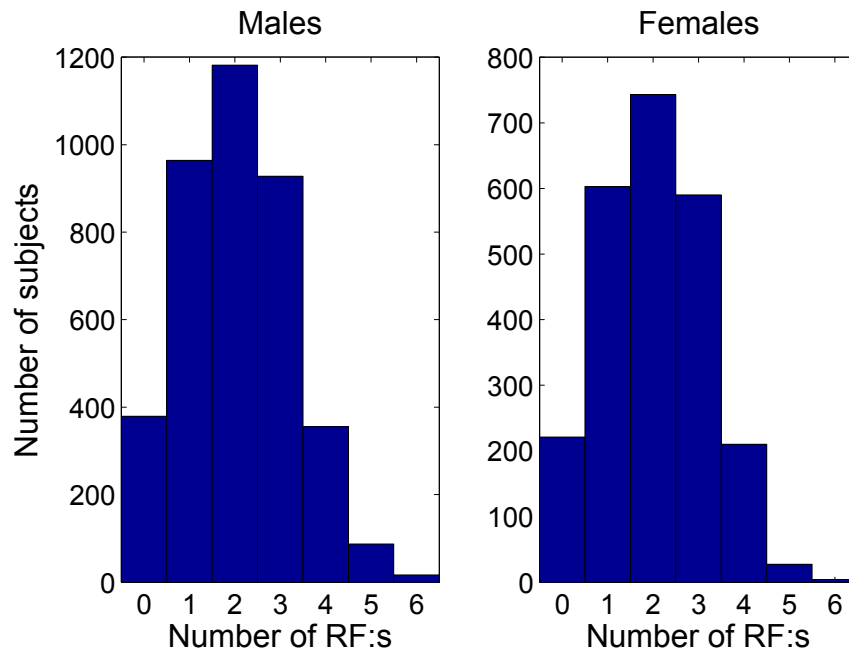


Fig. 2. Comparison of number of risk factors (family history of coronary artery disease, diabetes mellitus, smoking, hypertension, dyslipidaemia and obesity) by gender. RF, risk factors.

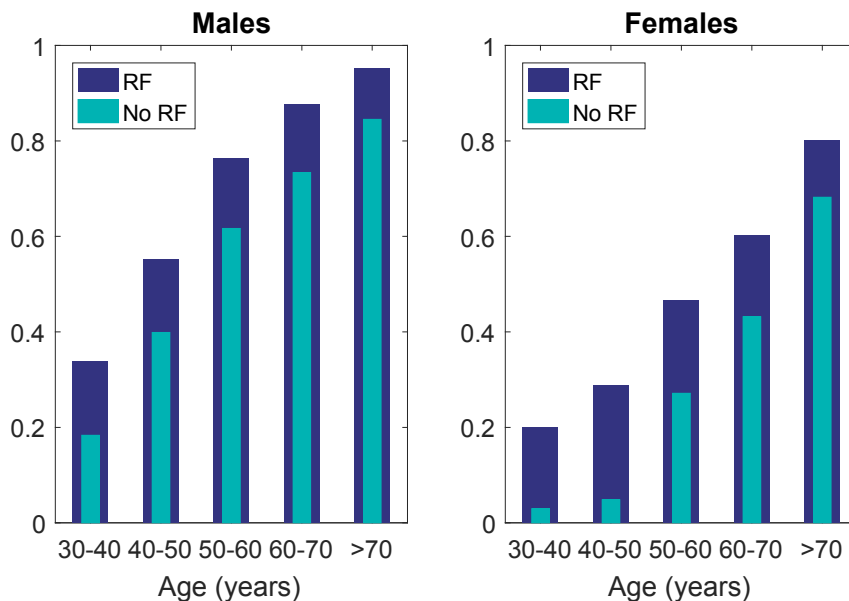


Fig. 3. Comparison of the proportion of patients with CAC in different age groups by gender, analysed according to the presence or absence of at least one of the four modifiable risk factors (smoking, diabetes mellitus, hypertension and/or dyslipidaemia). RF, presence of one or more of the four risk factors; No RF, absence of all four risk factors.

hypertension, dyslipidaemia, obesity and number of risk factors were all predictive of $CAC > 0$, $CAC \geq 100$ and $CAC \geq 400$, smoking proved not to be predictive among those with $CAC \geq 1000$. Results were similar for females, except that family history of CAD was never a predictor of CAC in any subgroup and smoking remained predictive in those with $CAC \geq 1000$. While all risk factors, including the number of risk factors, predicted CAC in all subgroups, obesity became borderline significant in patients with $CAC \geq 100$.

3.3. Multivariate risk factor prediction of CAC presence

Multivariate logistic regression analysis (Table 4) was performed to identify risk factors predictive of a CAC score >0 , ≥ 100 , ≥ 400 and ≥ 1000 compared to zero CAC by using backwards elimination in all patients with full data sets ($n = 5851$) to remove non-significant factors in a two-step process, having corrected for age. In the first step, all risk factors were included (age, family history of CAD, smoking, diabetes mellitus, hypertension, dyslipidaemia and obesity); after removal of subjects with incomplete data, 2339

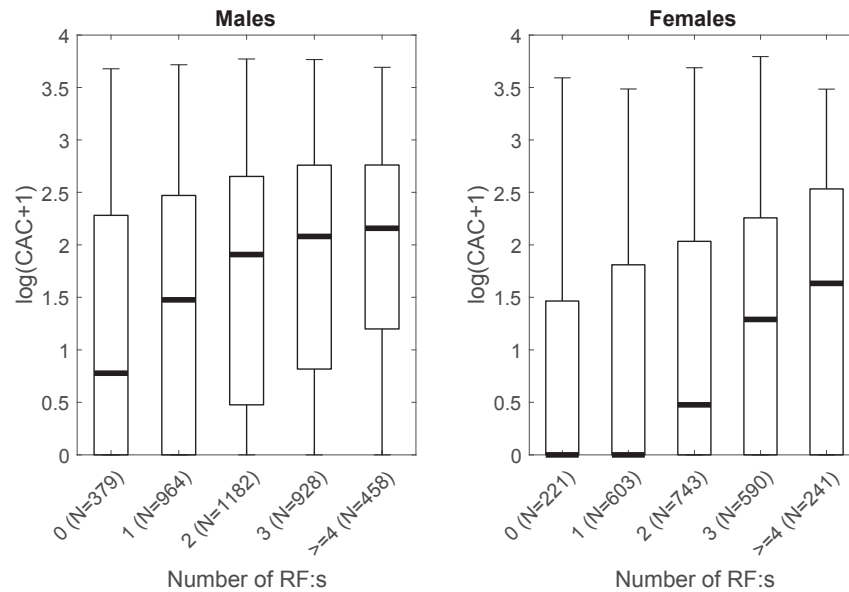


Fig. 4. Boxplots showing range, 75%, 50% (median) and 25% quartiles for all subjects (including those with CAC = 0).

Table 3
Univariate risk factor predictors in males and females using logistic regression to predict the risk of (a) CAC presence vs. zero CAC; (b) CAC ≥ 100 vs. zero CAC; (c) CAC ≥ 400 vs. zero CAC; and (d) CAC ≥ 1000 vs. zero CAC.

Risk factors	Males			Females		
	β	OR (95% CI)	p	β	OR (95% CI)	p
(a) CAC > 0	n = 3911, 74% with CAC > 0			n = 2398, 53% with CAC > 0		
Family history of CAD	0.34	1.41 (1.20–1.66)	<0.001	0.03	1.03 (0.86–1.23)	0.76
Smoking	0.22	1.24 (1.05–1.47)	0.01	0.63	1.88 (1.53–2.30)	<0.001
Diabetes mellitus	0.69	1.99 (1.51–2.62)	<0.001	1.03	2.79 (2.09–3.73)	<0.001
Hypertension	0.53	1.70 (1.44–2.00)	<0.001	0.37	1.44 (1.20–1.73)	<0.001
Dyslipidaemia	0.72	2.05 (1.73–2.42)	<0.001	0.35	1.42 (1.19–1.70)	<0.001
Obesity	0.28	1.33 (1.03–1.71)	0.03	0.38	1.47 (1.08–2.00)	0.01
Number of risk factors	0.44	1.56 (1.46–1.66)	<0.001	0.38	1.47 (1.36–1.59)	<0.001
(b) CAC ≥ 100	n = 2805, 64% with CAC ≥ 100			n = 1776, 36% with CAC ≥ 100		
Family history of CAD	0.48	1.61 (1.13–1.96)	0.001	−0.05	0.95 (0.76–1.19)	0.65
Smoking	0.24	1.28 (1.05–1.55)	0.01	0.65	1.91 (1.47–2.48)	<0.001
Diabetes mellitus	0.96	2.62 (1.95–3.52)	<0.001	1.38	3.96 (2.85–5.51)	<0.001
Hypertension	0.62	1.86 (1.54–2.24)	<0.001	0.50	1.66 (1.31–2.09)	<0.001
Dyslipidaemia	0.84	2.31 (1.91–2.80)	<0.001	0.41	1.51 (1.20–1.89)	0.001
Obesity	0.31	1.36 (1.01–1.84)	0.05	0.35	1.42 (0.96–2.11)	0.08
Number of risk factors	0.61	1.83 (1.69–1.98)	<0.001	0.49	1.63 (1.48–1.80)	<0.001
(c) CAC ≥ 400	n = 2035, 51% with CAC ≥ 400			n = 1422, 21% with CAC ≥ 400		
Family history of CAD	0.42	1.52 (1.21–1.92)	<0.001	−0.08	0.92 (0.69–1.25)	0.61
Smoking	0.35	1.42 (1.13–1.78)	0.003	0.70	2.02 (1.43–2.86)	<0.001
Diabetes mellitus	1.09	2.96 (2.13–4.11)	<0.001	1.69	5.40 (3.65–8.00)	<0.001
Hypertension	0.67	1.96 (1.57–2.45)	<0.001	0.74	2.09 (1.51–2.90)	<0.001
Dyslipidaemia	0.78	2.18 (1.74–2.74)	<0.001	0.47	1.60 (1.12–2.15)	0.002
Obesity	0.45	1.57 (1.11–2.23)	0.01	0.71	2.03 (1.22–3.41)	0.007
Number of risk factors	0.68	1.98 (1.80–2.18)	<0.001	0.64	1.90 (1.66–2.18)	<0.001
(d) CAC ≥ 1000	n = 1452, 31% with CAC ≥ 1000			n = 1258, 10% with CAC ≥ 1000		
Family history of CAD	0.41	1.51 (1.12–2.04)	0.007	−0.08	0.92 (0.60–1.40)	0.69
Smoking	0.19	1.21 (0.89–1.64)	0.21	1.20	3.32 (2.07–5.32)	<0.001
Diabetes mellitus	1.59	4.90 (3.34–7.20)	<0.001	1.72	5.61 (3.33–9.46)	<0.001
Hypertension	0.82	2.26 (1.69–3.03)	<0.001	0.76	2.13 (1.32–3.42)	0.002
Dyslipidaemia	0.73	2.08 (1.55–2.79)	<0.001	0.53	1.70 (1.11–2.58)	0.01
Obesity	0.68	1.97 (1.26–3.08)	0.003	0.78	2.18 (1.08–4.39)	0.03
Number of risk factors	0.74	2.09 (1.84–2.36)	<0.001	0.75	2.12 (1.75–2.56)	<0.001

CAC, CAC score; CAD, coronary artery disease.

males and 1218 females remained. This analysis showed that there was a non-significant influence of obesity in both genders; obesity was therefore removed. In all patients with complete data (3624 males and 2227 females), backwards elimination removed family history of CAD in females, dyslipidaemia in females with CAC ≥ 400

and ≥ 1000 and smoking in males with CAC ≥ 1000 . All other risk factors had a significant influence in both genders.

The most important dichotomous predictors of CAC presence in males were dyslipidaemia and diabetes ($\beta = 0.64$ and 0.63 respectively) and for increasing CAC scores diabetes was the most

Table 4

Multivariate predictors of (a) CAC presence vs. zero CAC, (b) CAC $\geq$ 100 vs. zero CAC, (c) CAC $\geq$ 400 vs. zero CAC, and (d) CAC $\geq$ 1000 vs. zero CAC in males and females using the logistic regression model with backwards elimination.

Risk factors	Males			Females		
	β	OR (95% CI)	p value	β	OR (95% CI)	p value
(a) CAC > 0	n = 3624, 74% with CAC > 0			n = 2227, 53% with CAC > 0		
Age	0.09	1.09 (1.08–1.10)	<0.001	0.08	1.08 (1.07–1.10)	<0.001
Family history of CAD	0.30	1.35 (1.14–1.60)	0.001			
Smoking	0.19	1.20 (1.01–1.43)	0.04	0.68	1.97 (1.59–2.44)	<0.001
Diabetes mellitus	0.63	1.88 (1.40–2.53)	<0.001	1.08	2.94 (2.14–4.05)	<0.001
Hypertension	0.39	1.47 (1.24–1.75)	<0.001	0.30	1.35 (1.11–1.64)	0.003
Dyslipidaemia	0.64	1.90 (1.60–2.25)	<0.001	0.30	1.34 (1.11–1.62)	0.002
(b) CAC $\geq$ 100	n = 2586, 63% with CAC $\geq$ 100			n = 1641, 36% with CAC $\geq$ 100		
Age	0.12	1.13 (1.12–1.14)	<0.001	0.11	1.11 (1.10–1.13)	<0.001
Family history of CAD	0.46	1.58 (1.29–1.95)	<0.001			
Smoking	0.23	1.26 (1.02–1.55)	0.03	0.74	2.09 (1.58–2.75)	<0.001
Diabetes mellitus	0.97	2.64 (1.90–3.66)	<0.001	1.39	4.01 (2.78–5.77)	<0.001
Hypertension	0.40	1.49 (1.21–1.82)	<0.001	0.36	1.44 (1.11–1.85)	0.005
Dyslipidaemia	0.79	2.20 (1.80–2.69)	<0.001	0.32	1.37 (1.08–1.75)	0.01
(c) CAC $\geq$ 400	n = 1872, 49% with CAC $\geq$ 400			n = 1318, 20% with CAC $\geq$ 400		
Age	0.13	1.14 (1.13–1.16)	<0.001	0.12	1.12 (1.10–1.15)	<0.001
Family history of CAD	0.42	1.52 (1.19–1.94)	0.001			
Smoking	0.33	1.39 (1.09–1.78)	0.009	0.77	2.16 (1.49–3.13)	<0.001
Diabetes mellitus	1.08	2.95 (2.06–4.24)	<0.001	1.63	5.08 (3.31–7.80)	<0.001
Hypertension	0.46	1.59 (1.25–2.03)	<0.001	0.54	1.71 (1.20–2.44)	0.003
Dyslipidaemia	0.70	2.02 (1.59–2.58)	<0.001			
(d) CAC $\geq$ 1000	n = 1336, 29% with CAC $\geq$ 1000			n = 1170, 10% with CAC $\geq$ 1000		
Age	0.14	1.15 (1.13–1.17)	<0.001	0.13	1.15 (1.12–1.18)	<0.001
Family history of CAD	0.39	1.48 (1.06–2.05)	0.02			
Smoking				1.22	3.40 (2.07–5.56)	<0.001
Diabetes mellitus	1.60	4.93 (3.21–7.56)	<0.001	1.76	5.81 (3.31–10.2)	<0.001
Hypertension	0.64	1.89 (1.36–2.63)	<0.001	0.60	1.82 (1.08–3.07)	0.02
Dyslipidaemia	0.63	1.87 (1.36–2.58)	<0.001			

CAC, CAC score; CAD, coronary artery disease; age, actual age in years.

important, followed by dyslipidaemia; hypertension was only an important predictor for those with CAC $\geq$ 1000. Among females, the most important predictors of CAC presence were diabetes followed by smoking (β = 1.08 and 0.68 respectively) and these risk factors remained the most important predictors with increasing CAC scores.

3.4. Multivariate predictors of CAC presence by gender and age group

Table 5 shows the multivariate independent predictors of CAC presence analysed by gender and age groups <50 years, 50–70 years and $\geq$ 70 years, in 5851 patients. This demonstrates that in patients aged <50 and 50–70 years, the predictive risk factors were the same. In males, diabetes, hypertension and dyslipidaemia are

Table 5

Multivariate predictors of CAC presence by gender and age group.

Risk factors	Males with CACS > 0 (n = 3624)			Females with CACS > 0 (n = 2227)		
	B	OR (95% CI)	p-value	B	OR (95% CI)	p-value
Age < 50 years (Males n = 886; Females n = 375)						
Smoking				0.57	1.76 (1.02–3.06)	0.04
Diabetes mellitus	0.67	1.96 (1.10–3.49)	0.02	1.96	7.08 (3.24–15.5)	<0.001
Hypertension	0.39	1.48 (1.11–1.98)	0.007	0.74	2.09 (1.20–3.67)	0.01
Dyslipidaemia	0.84	2.32 (1.75–3.07)	<0.001	0.64	1.89 (1.07–3.34)	0.03
Age 50–70 years (Males n = 2102; Females n = 1305)						
Smoking				0.50	1.65 (1.29–2.11)	<0.001
Diabetes mellitus	0.66	1.93 (1.34–2.77)	<0.001	0.76	2.13 (1.46–3.11)	<0.001
Hypertension	0.59	1.80 (1.44–2.24)	<0.001	0.33	1.39 (1.10–1.74)	0.005
Dyslipidaemia	0.52	1.69 (1.35–2.11)	<0.001	0.33	1.40 (1.12–1.75)	0.003
Age $\geq$ 70 years (Males n = 636; Females n = 547)						
Smoking				1.12	3.07 (1.54–6.11)	0.001
Diabetes mellitus				1.05	2.86 (1.43–5.71)	0.001
Dyslipidaemia	0.79	2.20 (1.12–4.32)	0.02			

CACS, CAC score; CAD, coronary artery disease.

predictive, with diabetes being the most important in both age groups. In females, the same risk factors were predictive, with the addition of smoking; diabetes was also the most important risk factor in females in both age groups. In males aged ≥ 70 years, however, only dyslipidaemia was predictive, while in females aged ≥ 70 years both smoking and diabetes were predictive, with smoking being the more important one.

4. Discussion

Our results show that in 6309 symptomatic patients, males were more likely to have CAC in all age groups, with more males having CAC than not above age 50 years, while there were more females with CAC than without above age 60 years. In both genders, the median and interquartile CAC scores increased with number of risk factors but a few patients had relatively high CAC and no risk factors. Since approximately 85% of patients received angiography (either conventional or CTCA), as reported in our previous publication which examined this cohort of patients [12], it could be expected that several of the zero CAC patients would have had incipient CAC.

Multivariate regression analysis shows that age, dyslipidaemia, hypertension, diabetes and smoking were independent predictors of CAC presence in males and females, with the addition of family history of CAD in males; obesity was not predictive in either gender. The same risk factors were predictive of increasing CAC scores, with the exception of dyslipidaemia for CAC scores ≥ 400 and smoking in males for CAC scores ≥ 1000 . The most important dichotomous predictors of CAC presence in males were dyslipidaemia and diabetes ($\beta = 0.64$ and 0.63 respectively) and, for increasing CAC scores, diabetes was the most important, followed by dyslipidaemia; hypertension was only an important predictor for those patients with CAC ≥ 1000 . Among females, the most important predictors of CAC presence were diabetes followed by smoking ($\beta = 1.08$ and 0.68 respectively), and these risk factors remained the most important predictors with increasing CAC scores.

When broken down into age groups, in both males and females aged < 70 years, diabetes, hypertension and dyslipidaemia were predictive, with diabetes being the strongest factor; in females aged < 70 years, smoking was also predictive. There was no difference in predictive risk factors between those aged < 50 and $50-70$ years. Among those aged ≥ 70 years, results are completely different, with only dyslipidaemia being predictive in males, but smoking and diabetes were predictive in females.

Thus, it is clear that up to age 70 years, there is little difference in the impact of individual risk factors between males and females, although females lag males by around 10 years with respect to incidence. At age 70 years or above, the predictive risk factors are fewer and differ between males and females. This decline in the number of risk factors predicting the presence of CAC above the age of 70 years, irrespective of gender, indicates the role of age as a main predictor. Thus, the decline in the power of risk factors in patients aged > 70 years indicates the important role of age as a predictor in this age group.

Not many studies have investigated the association between risk factors and CAC presence in symptomatic patients. Atar et al. studied 442 Turkish patients and found that smoking and the Framingham risk score (comprising age, gender, LDL and HDL cholesterol, smoking, blood pressure and diabetes) independently predicted CAC presence, as well as serum uric acid [13]; however, because the Framingham risk score was used rather than individual risk factors, we cannot directly compare the data. Greif et al. investigated 1560 European patients and showed that diabetes, dyslipidaemia (as statin use) and lipoprotein (a) were independent predictors of CAC presence [14]. Nevertheless, in our multivariate

analyses, dyslipidaemia and diabetes in males were also predictors of CAC presence in agreement with Greif et al. Ehara et al. investigated the risk factors for zero CAC among 309 symptomatic patients and found that the absence of dyslipidaemia and diabetes was independently predictive in men but not in women [15]; this would suggest that the presence of these risk factors may be predictive of CAC presence in males, although other risk factors may also be predictive. This is broadly in line with our results for males, which showed that dyslipidaemia and diabetes were the strongest risk factors, and those of Greif et al. in a 72% male cohort. Nevertheless, our results show that these risk factors were predictive in females as well. More recently, Ovrehus et al. have shown that in 2257 symptomatic patients, mean age 55.5 years, 45% male, age, male gender, hyperlipidaemia, hypertension, smoking and family history of CAD were independent predictors of CAC presence, with male gender having the highest risk [16]. Although they did not analyse by gender, Ovrehus et al.'s results are broadly in line with ours.

Although Ehara et al. divided their sample by gender, none of the four studies of symptomatic patients described above assessed the risk factors by age group. However, in a study of asymptomatic subjects, Detrano et al. used age 65 years as a threshold and found that among 1461 high-risk subjects, with a mean age of 63 years, 88% of whom were male, a family history of premature myocardial infarction or death was the only predictor of CAC presence in both age groups, while diabetes was predictive only in those aged < 65 years and smoking and low HDL were predictive only in those aged ≥ 65 years [17], which is somewhat at variance with our results and studies of symptomatic patients. Amongst the many other studies of asymptomatic subjects, which do not analyse their sample by age group or gender, the DanRisk study showed that gender, smoking, diabetes, hypercholesterolaemia, hypertension and family history of CVD were all independently predictive [18].

Among studies of symptomatic patients, our findings concur with most published evidence that together with age, dyslipidaemia and diabetes are the most important predictors of CAC presence in males or in cohorts which are predominantly male. Our findings also agree with Detrano et al. that at age 65–70 years some risk factors may cease to be predictive, while others become predictive. Therefore, we believe that our findings are of significant importance for three reasons. Firstly, because of our large sample volume of 6309 patients, ours is by far the largest cohort of symptomatic patients. Secondly, we investigated a multinational cohort of patients from six countries and two continents and thirdly, we studied the impact of both age and gender, not covered by any other study.

Our study has some limitations. We relied on the risk factor assessments performed by the investigating centres rather than by our own core lab, but we believe that they should be substantially accurate. Data on whether patients had typical or atypical angina and duration of risk factors were not available and might have had a bearing on their predictive ability. Patients with typical angina would invariably have been sent for an invasive angiogram, whereas those receiving CTCA are likely to have had atypical angina. The lack of difference in risk factor prediction of CAC beyond a score of 100 was not analysed in this study as it was not part of the objective. Despite the lack of data for obesity in all patients, analysis of those with data did not demonstrate any predictive value for obesity. There are likely to be additional confounding factors; Atar et al. found that serum uric acid was predictive [13], while lipoprotein (a) was also predictive in the study by Greif et al. [14]. We have also previously shown that elements of the diet can be predictive [19]. Although large studies such as the Multiethnic Study of Atherosclerosis (MESA), the Heinz Nixdorf Recall study (HNR) and DanRisk have reported

relationships between risk factors and CAC, we believe that direct comparison with our finding cannot be justified, as these cohorts were population-based with asymptomatic subjects, whereas ours were symptomatic patients. The slight difference in the prevalence of patients with CAC in the elderly compared to prevalence in asymptomatic population studies could be explained on the basis of selection bias.

Our analysis has shown that predictive risk factors for CAC presence include dyslipidaemia, hypertension, diabetes and smoking, which are all modifiable risk factors, either by medication or diet and lifestyle changes. Only family history of CAD, which was mildly predictive in males, is not susceptible to modification. Our results also show that individual risk factors have a different degree of impact depending on age and gender, a finding that should have direct clinical application in atherosclerosis prevention clinics.

In conclusion, although most risk factors, excluding obesity in both genders and family history of CAD in females, are predictive of CAC presence in males and females, our study clearly demonstrates the importance of diabetes and dyslipidaemia in predicting increasing CAC scores in males and diabetes and smoking in females. Furthermore, the risk factor predictors of CAC presence in symptomatic patients are influenced by age and gender. In patients aged <70 years, diabetes, hypertension and dyslipidaemia were predictive in both genders, with smoking also being predictive in females. Among those aged ≥70 years, only dyslipidaemia was predictive in males but smoking and diabetes were predictive in females. The reduced number of risk factors predicting CAC in the older age group supports the important role of age in predicting CAC presence in symptomatic patients, as has been shown elsewhere in asymptomatic subjects.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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