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Cardiovascular Risk Factors and Coronary Calcification in a Middle-aged Dutch Population

The ImaLife Study

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Purpose: To assess the presence of coronary artery calcium (CAC) and its association with cardiovascular risk factors and Systematic COronary Risk Evaluation (SCORE) risk in a middle-aged Dutch population.

Methods: Classic cardiovascular risk factors and CAC were analyzed in 4083 participants aged 45 to 60 years (57.9% women) from the population-based ImaLife study. CAC scores were quantified on noncontrast cardiac CT scans. Age-specific and sex-specific distribution of CAC categories (0, 1 to 99, 100 to 299, ≥300) and percentiles were determined. SCORE risk categories (<1%, ≥1% to 5%, and ≥5%) were compared with CAC distribution. Population attributable fractions (PAFs) of classic risk factors for CAC were estimated.

Results: CAC was present in 54.5% male and 26.5% female participants. The percentage of individuals with CAC increased with increasing age. Mean SCORE was 2.0% in men and 0.7% in women. In SCORE <1%, 32.7% of men and 17.1% of women had CAC. In men with SCORE ≥5%, 26.9% had no CAC. Only 0.1% of women had SCORE ≥5%. PAF of classic risk factors for CAC was 18.5% in men and 31.4% in women. PAF was highest for hypertension (in men 8.0%, 95% confidence interval, 4.2%-11.8%; in women 13.1%, 95% confidence interval, 7.9%-18.2%) followed by hypercholesterolemia and obesity.

Conclusion: In this middle-aged cohort, more than half of the men and a quarter of the women had CAC. One out of 4 men at high risk (SCORE ≥5%) could be placed into a lower risk category owing to absence of CAC. Thus, adding CAC scoring to SCORE could have considerable effect on cardiovascular risk classification. Elimination of exposure to classic risk factors could reduce limited proportion of CAC in a middle-aged population.

Key Words: coronary artery calcium score, risk factors, coronary heart disease, population attributable fraction, systematic coronary risk evaluation

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Cardiovascular disease (CVD) is a leading cause of death in the world; in Europe, >4 million people die owing to CVD each year.[1] More efforts are needed to detect individuals at high risk for CVD and to implement prevention and early treatment. Systematic COronary Risk Evaluation (SCORE) risk charts based on sex, age, smoking behavior, systolic blood pressure, and blood cholesterol are recommended to assess a 10-year risk of fatal CVD for primary prevention in Europe.[2] Coronary artery calcium (CAC) score can improve risk prediction of coronary artery disease (CAD).[3–8] Adding CAC scores as a risk modifier to SCORE may further improve risk classification, especially for individuals with a SCORE risk around a decisional threshold (eg, 5%).[2]

Reference values for CAC cutoffs and CAC-based risk reclassification rates are 2 prerequisites before CAC scoring can be applied in primary prevention strategies. The first requirement can be met by establishing population-based CAC cutoffs by age and sex, in particular in the middle-aged population in which the lifetime effect of preventive treatment will be largest. However, so far only few studies reported CAC distribution for middle-aged populations in European low-risk countries.[9,10] The latter prerequisite may be estimated by a comparison of differences in risk classification as based on risk factors or SCORE categorization versus CAC-based risk classification. Thus far, only the DanRisk study has compared CAC-based risk classification to SCORE categorization. In this study, it was shown that CAC was detected in 37% of healthy individuals who had low SCORE (<5%), whereas 32% of individuals did not have CAC despite high SCORE (≥5%). However, this study had a relatively small sample size with discrete age groups that did not represent a general middle-aged population.[10]

CAC score is an imaging marker of coronary atherosclerotic burden, which reflects the accumulated effect of long-time exposure to all known and unknown risk factors and can assess coronary age.[11] Prior studies have reported that classic cardiovascular risk factors are associated with

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CAC.[12–16] However, no study has yet investigated the proportion of CAC that can be attributed to classical risk factors. CAC can be considered as an intermediate between risk behavior and final cardiovascular outcome. Knowledge about the relation between classic risk factors for cardiovascular outcome and CAC score might help to better understand strategies to prevent high CAC scores and related cardiovascular events. A useful measure is the population attributable fraction (PAF), which estimates the proportion of the present of CAC that would be reduced by eliminating exposure to a risk factor.

In a middle-aged Dutch population, we aimed (1) to describe age-specific and sex-specific distribution of CAC scores, (2) to evaluate the effect of CAC scoring on risk classification as based on the SCORE method, and (3) to assess the extent of CAC presence that is attributable to cardiovascular risk factors.

METHODS

Study Population and Setting

The ImaLife study is an ongoing study embedded in the Lifelines cohort,[17] which was designed to establish reference values of imaging biomarkers for early stages of the big three diseases: CAD, lung cancer, and chronic obstructive pulmonary disease.[18] In brief, the Lifelines cohort was launched in 2006 (baseline round) to collect data from physical examinations; laboratory tests; and questionnaires on general demographics, health status, lifestyle, and environmental factors. Generally, every 1.5 years, follow-up questionnaires on aforementioned aspects were administered, and every 5 years, follow-up assessments were scheduled for renewed physical examinations and laboratory tests. The second round assessment was performed from 2014 to 2017. Lifelines participants, who had completed the second round assessment including lung function testing, were invited for the ImaLife study, and after informed consent, underwent a low-dose computed tomography (CT) examination of the chest. The ImaLife study was approved by the medical ethics committee of the University Medical Center Groningen, the Netherlands. CT scan acquisition started in August 2017 and focused initially on the middle-aged population.

For the purpose of this study, 4157 participants, aged 45 to 60 years at the time of the CT scan, were consecutively enrolled from inception until February 2019. Participants in whom the CT images revealed cardiac intervention or who had a history of CAD were excluded from the analysis (n = 74). History of CAD was defined as self-reported history of myocardial infarction, and/or coronary artery bypass grafting or percutaneous coronary intervention, and/or signs of myocardial infarction on electrocardiography. Thus, 4083 participants free of prior diagnosed CAD were included in this study.

Assessment of Cardiovascular Risk Factors

In the Lifelines cohort, questionnaires on health status and lifestyle, including smoking habits, were collected at baseline and updated during follow-up questionnaires. Information on demographics and medication use was collected by questionnaires at baseline. Type of medication was recorded in the database using anatomic therapeutic chemical codes. Blood pressure measurements, laboratory blood tests, and anthropometric measurements were conducted during the baseline and second round visit, as previously reported in detail.[19] For all risk factor definitions, the most recent assessment was used, supplemented with information from prior assessments in case of missing information.

Risk factor phenotypes were defined based on the self-reported health status, use of medication, and physical examinations or laboratory tests both at baseline and in follow-up rounds. The following were considered as classic cardiovascular risk factors: current smoking, hypertension, hypercholesteremia, diabetes, and obesity. Current smoking was defined as having smoked within the past 30 days. Hypertension was defined as self-reported hypertension, systolic blood pressure $\geq$ 140, diastolic blood pressure $\geq$ 90 mm Hg, and/or use of antihypertensive medication.[19] Hypercholesterolemia was defined as serum total cholesterol $\geq$ 6.2 mmol/L and/or use of lipid-lowering medication.[20] Diabetes was defined as self-reported diabetes, fasting glucose $\geq$ 7.0 mmol/L, nonfasting glucose $\geq$ 11.1 mmol/L, glycated hemoglobin A1c $\geq$ 7.0%, and/or use of oral antidiabetic medication or insulin.[19,21] Body mass index was calculated [weight (kg)/height (m^2)], using anthropometric measurements at the second round assessment; obesity was defined as body mass index $\geq$ 30 kg/m^2. Individuals who were identified as having hypertension, hypercholesterolemia, or diabetes at a given round assessment were considered as having hypertension, hypercholesterolemia, or diabetes. Participants were categorized by number of classic risk factors (0, 1, 2, $\geq$ 3 risk factors).

The Dutch low-risk SCORE chart was used to calculate the 10-year risk of fatal CVD based on classic risk factors (age, sex, smoking status, systolic blood pressure, and ratio of total cholesterol to high-density lipoprotein cholesterol).[21] In this study, participants with known diabetes (n = 132) were (only) excluded from the analysis which involved SCORE. This is because recent ESC guidelines do not recommend the use of the SCORE risk chart in individuals with diabetes owing to the known high CVD risk and instead recommend intensive risk factor modification by medication.[2] SCORE could not be calculated in 66 participants owing to missing covariates in the second assessment. SCORE was stratified into low (< 1%), moderate ($\geq$ 1% to 5%), and high ($\geq$ 5%) risk levels for the analyses.[2]

Measurement of CAC

Noncontrast cardiac CT scanning for CAC scoring was performed with a third-generation dual-source CT scanner (Somatom Force, Siemens Healthineers, Germany) with prospective electrocardiography -triggering. A tube voltage of 120 kVp and tube current of 64 quality reference mAs/rot were used. Images were reconstructed with a slice thickness and increment of 3.0 and 1.5 mm. CAC was quantified using the Agatston method[22] with dedicated software (Syngo.via VB30A, CaScoring, Siemens) by a well-trained researcher. The Agatston score was categorized into very low (0), mildly increased (1 to 99), moderately increased (100 to 299), and severely increased ($\geq$ 300) risk.[23]

Statistical Analysis

Descriptive statistics were used to summarize the population characteristics. Presence of CAC was defined as CAC score > 0. Differences in characteristics and SCORE risk between men and women were compared using independent *t* test or Mann-Whitney *U* test for continuous variables depending on the distribution, and χ^2 test for categorical variables. Association between each risk factor and presence of CAC was assessed using a logistic regression model that first was only adjusted for age. Thereafter, a fully adjusted logistic regression model was created by entering the following covariates: age, current smoking, hypertension, hypercholesteremia, diabetes, and obesity. All logistic regression models were stratified by sex. Odds ratio (OR) with 95% confidence interval (CI) was reported for the estimation of coefficient effects. *C*-statistics was used to evaluate

the goodness of fit for each model. PAF was estimated using the R package AF as previously described,[24] and a fully adjusted logistic model was used to account for potential confounding effects. Overall PAF was calculated using the following formula[25] :PAFoverall = 1 – [(1 – PAF1)(1 – PAF2)(1 – PAF3)…]. In this study sample, information on 1 classic risk factor was missing in 0.07% (3/4,083) of the cases; the list-wise deletion method was used for dealing with these missing values. All statistical analyses were conducted using R (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria). Significance level was a 2-tailed *P*-value of <0.05.

RESULTS

Characteristics of Study Population

In total, 4083 middle-aged (45 to 60 y) participants from the ImaLife study were included, comprising 57.9% women. Population characteristics stratified by sex are shown in Table 1. The mean age was similar for sex. Men were more often current smokers than women and had a higher prevalence of hypertension and hypercholesterolemia.

CAC Distribution

Prevalence of CAC was 54.5% in men and 26.5% in women. In subjects with CAC, also the median CAC score was higher in men than in women (32 vs. 20, $P < 0.001$). Table 2 shows the CAC percentiles and risk categorization by age for men and women. Prevalence of CAC and CAC scores in the 75th and 90th percentiles increased with age.

TABLE 1. Characteristics of study population by sex

Characteristics	Men (n = 1720)	Women (n = 2363)	*P*
Age (y)	53.2 ± 4.5	53.0 ± 4.6	0.173
White race (%)	98.5	98.6	0.885
Married (%)	88.6	85.2	0.002
Current smoking (%)	29.2	22.3	< 0.001
SBP (mm Hg)	131.1 ± 14.2	124.1 ± 15.6	< 0.001
DBP (mm Hg)	78.7 ± 9.5	72.4 ± 9.0	< 0.001
Antihypertensive medication (%)	19.9	17.1	0.192
Hypertension (%)	44.2	33.9	< 0.001
Total cholesterol (mmol/L)	5.3 ± 1.0	5.2 ± 0.9	< 0.001
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.7 ± 0.4	< 0.001
LDL cholesterol (mmol/L)	3.6 ± 0.9	3.3 ± 0.9	< 0.001
Lipid-lowering medication (%)	10.4	4.2	< 0.001
Hypercholesterolemia (%)	25.3	17.2	< 0.001
Diabetes (%)	3.9	2.8	0.051
BMI (kg/m^2)	26.5 ± 3.4	25.8 ± 4.4	< 0.001
Obesity (%)	14.0	15.5	0.204
No. classic risk factors (%)			< 0.001
0	30.0	38.4	
1	35.5	37.9	
2	24.5	18.1	
≥ 3	10.0	5.6	
SCORE (% 10-year risk)	2.0 ± 1.5	0.7 ± 0.5	< 0.001
SCORE categories (%)			< 0.001
< 1%	6.6	58.5	
1%-5%	87.0	41.4	
≥ 5%	6.4	0.1	

Values are mean and SD or percentage.

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Associations With Cardiovascular Risk Factors

In this study (n = 4080, as 3 were missing risk factor information), classic cardiovascular risk factors were absent in 34.8% of the study population, whereas 7.4% of participants had ≥ 3 risk factors. A higher proportion of men compared with women had ≥ 3 risk factors (10.0% vs. 5.6%, $P < 0.001$). Correspondingly, fewer men had zero risk factors compared with women (30% vs. 38.4%, $P < 0.001$). The distribution of CAC categories across the number of risk factors is shown in Figure 1.

In the subpopulation without diabetes (n = 3885), mean SCORE was 1.3%. Men had a higher mean SCORE than women (2.0% vs. 0.7%, $P < 0.001$). Prevalence and severity of CAC across SCORE strata are shown in Figure 2. The proportion of individuals with high CAC increased with increasing SCORE risk. CAC was absent in 26.9% of men with SCORE ≥ 5%. Only 2 women (0.1%) had SCORE ≥ 5%.

ORs reflecting the association between classic risk factors and CAC presence are listed in Table 3. In both men and women, hypertension, hypercholesterolemia, and obesity were associated with CAC in the fully adjusted model. Current smoking was associated with CAC presence in women, but not in men. The *C*-statistic of the fully adjusted model was 0.687 (95% CI, 0.662-0.712) in men and 0.696 (95% CI, 0.672-0.720) in women, indicating fair discriminating accuracy for identifying whether a subject has CAC.

Combined PAF of the classic risk factors for CAC was 18.5% in men and 31.4% in women. Estimated PAFs of classic risk factors are listed in the Table 4, showing that hypertension was the strongest risk factor associated with presence of CAC.

DISCUSSION

In this middle-aged Dutch population, slightly more than half of the men and a quarter of the women had CAC. Hypertension, hypercholesterolemia, and obesity were associated with CAC presence in both sexes. However, only a limited proportion of CAC presence was attributable to classical cardiovascular risk factors. Moreover, in low risk (SCORE <1%), 32.7% of men and 17.1% of women did have CAC, whereas in high risk (SCORE ≥ 5%), 26.9% of men had no CAC and would be reclassified into lower risk.

CAC prevalence and CAC score percentiles for the Dutch population from 45 to 60 years old were established. There have been some prior population imaging studies that have described the CAC distribution for a similar age range, in particular the Heinz Nixdorf Recall (HNR) study[9] and the Multi-Ethnic Study of Atherosclerosis (MESA).[26] In general, values of CAC percentiles were lower in our cohort than in HNR, but comparable to MESA. For instance, in our cohort, the CAC score in the 50th percentile was 10 in men aged 55 to 60 years. This value is lower than the CAC score of 51.6 that was reported in HNR,[9] but is comparable to the CAC score of 13 in the low-risk (10-y Framingham risk of <10%) White participants aged 55 to 64 years in MESA.[26] For women, the CAC score in the 50th percentiles was 0 for the age groups 45 to 49, 50 to 54, and 55 to 60 years; this is similar to the results in HNR (aged 45 to 49, 50 to 54, and 55 to 59 years) and in MESA (aged 45 to 54 and 55 to 64 years).[9,26] Apart from differences in geographical and racial make-up of the studies, there are also differences in risk factors and estimated cardiovascular risk. The prevalence of hypertension (55% vs. 38%), hypercholesterolemia (47% vs. 21%), and diabetes (6% vs. 3%) were lower in our study population compared with HNR.[9] The similarity in CAC percentile scores between our study

TABLE 2. Coronary Artery Calcium Score Distribution by Sex and Age

	Men			Women		
Age (y)	**45-49 (n = 430)**	**50-54 (n = 543)**	**55-60 (n = 747)**	**45-49 (n = 633)**	**50-54 (n = 729)**	**55-60 (n = 1001)**
CAC percentiles (AU)						
25th	0	0	0	0	0	0
50th	0	0	10	0	0	0
75th	5	20	82	0	0	8
90th	43	133	281	4	26	81
CAC categories (%)						
0	61.9	49.7	33.1	84.8	77.4	63.4
1-99	31.4	37.9	44.4	13.3	19.6	28.0
100-299	4.4	7.0	13.1	1.3	1.8	6.2
≥300	2.3	5.4	9.4	0.6	1.2	2.4

AU indicates Agatston units.

and the Framingham low-risk subset of MESA could be owing to the fact that in our study > 95% of the participants had SCORE risk below 5%.[26]

The 2016 ESC guidelines on the primary prevention of CVD recommend to consider CAC scoring in individuals with calculated SCORE risk around the decisional thresholds, such as 5%.[2] Prior prospective studies with cardiovascular outcomes showed that CAC scoring leads to a net reclassification improvement in risk stratification.[3,7] Differences in risk classification derived from risk factor-based SCORE categorization versus CAC-based risk assessment can give an idea of the size effect of adding CAC scoring in risk evaluation in a particular population. So far, only one study, the DanRisk study, in a middle-aged cohort has investigated the discrepancy between risk categorization based on CAC and SCORE. This study in middle-aged Danish individuals (n = 1152; 50 or 60 y of age) showed that 37% of participants with SCORE <5% had CAC, whereas

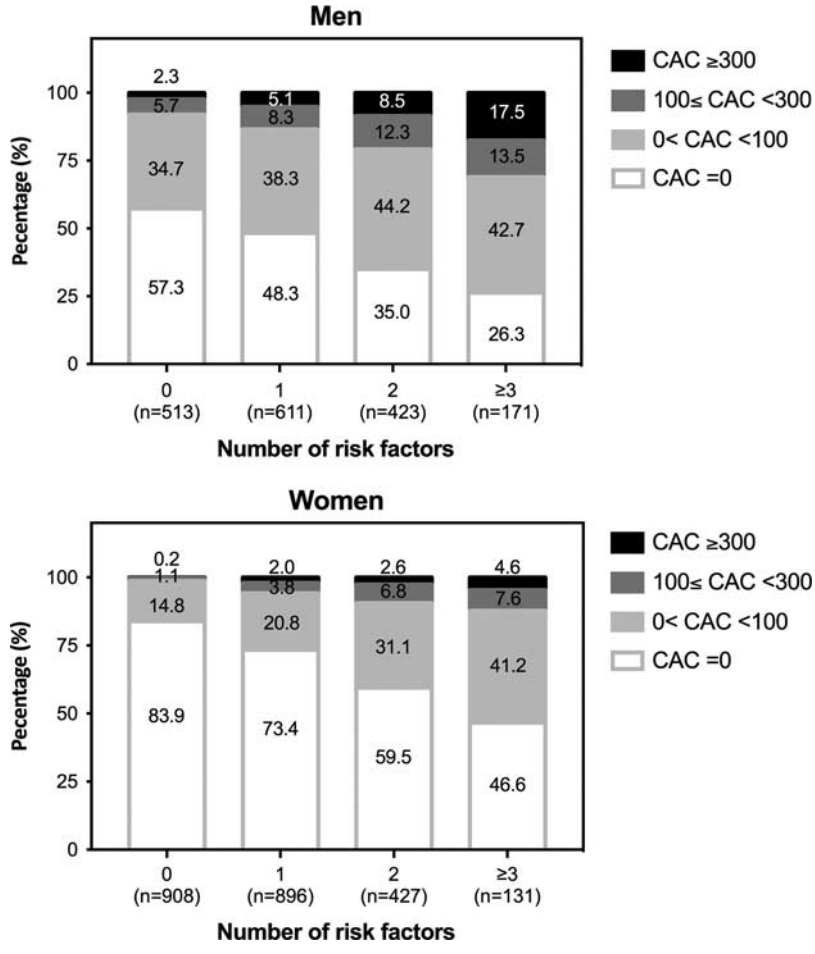

FIGURE 1. Categorical distribution of CAC by number of cardiovascular risk factors in men and women.

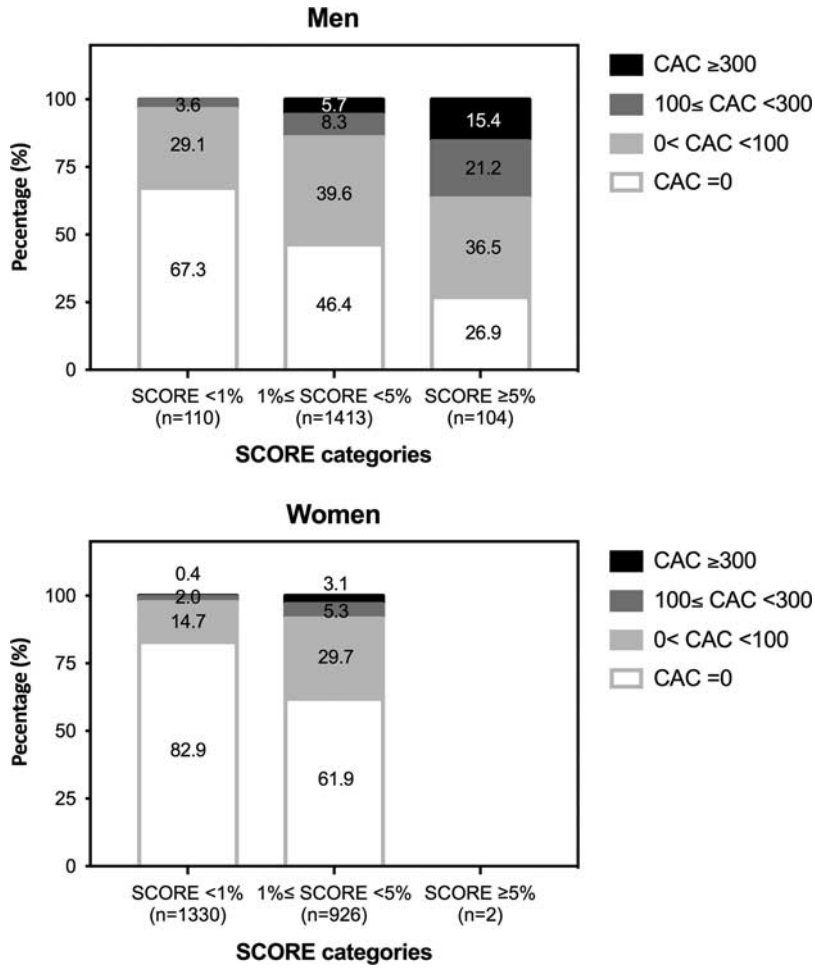

FIGURE 2. Prevalence of CAC score categories across SCORE strata in men and women. Percentages of coronary artery calcium score categories were not calculated in the group of women who had SCORE ≥ 5%, because only 2 women were in this group.

32% of participants with SCORE ≥ 5% had no CAC.[10] We observed similar results between risk categorization based on CAC and SCORE in the Dutch population, with 32.7% of men and 17.1% of women having CAC in SCORE <1%, whereas 26.9% of men had no CAC in SCORE ≥ 5%. These differences between SCORE and CAC scores in risk

TABLE 3. Associations Between Cardiovascular Risk Factors and Presence of Coronary Artery Calcium (n = 4080)

	Basic Regression Model*			Fully Adjusted Model†		
Risk Factors	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Men (n = 1718)						
Current smoking	1.19	0.96-1.48	0.112	1.10	0.88-1.38	0.397
Hypertension	1.75	1.43-2.14	< 0.001	1.56	1.27-1.92	< 0.001
Hypercholesterolemia	2.11	1.67-2.68	< 0.001	2.01	1.58-2.56	< 0.001
Diabetes	2.75	1.56-5.14	< 0.001	1.82	1.00-3.45	0.055
Obesity	1.92	1.43-2.59	< 0.001	1.66	1.23-2.26	0.001
Women (n = 2362)						
Current smoking	1.61	1.30-2.00	< 0.001	1.64	1.32-2.05	< 0.001
Hypertension	1.79	1.48-2.17	< 0.001	1.69	1.38-2.06	< 0.001
Hypercholesterolemia	1.92	1.52-2.41	< 0.001	1.84	1.45-2.32	< 0.001
Diabetes	2.44	1.46-4.06	< 0.001	1.71	0.99-2.91	0.051
Obesity	1.85	1.45-2.36	< 0.001	1.60	1.24-2.05	< 0.001

*Basic regression models were adjusted for age.
†Fully adjusted regression models were adjusted for age, current smoking, hypertension, hypercholesterolemia, diabetes and obesity.

TABLE 4. Population Attributable Fraction of Cardiovascular Risk Factors for Coronary Artery Calcium (n = 4080)

	Population Attributable Fraction*					
	Men (n = 1718)			Women (n = 2362)		
Risk Factors	PAF (%)	95% CI	*P*	PAF (%)	95% CI	*P*
Current smoking	1.1	0.0-3.7	0.394	7.8	4.1-11.4	< 0.001
Hypertension	8.0	4.2-11.8	< 0.001	13.1	7.9-18.2	< 0.001
Hypercholesterolemia	7.1	4.6-9.5	< 0.001	8.3	4.9-11.8	< 0.001
Diabetes	0.8	0.0-1.6	0.047	1.2	0.0-2.5	0.062
Obesity	2.8	1.1-4.5	0.001	5.5	2.3-8.7	< 0.001

*PAF was estimated based on the fully adjusted models with age, current smoking, hypertension, hypercholesterolemia, diabetes, and obesity.

classification suggest that the SCORE algorithm cannot completely differentiate participants who are at elevated risk of developing CAD, especially for a low-moderate risk group, and that the CAC score may have considerable added value in the middle-aged Dutch population. In the ongoing ImaLife study within Lifelines, with longitudinal records of cardiovascular events in the coming years, we will be able to confirm to what extent CAC scoring indeed stratifies for cardiovascular events beyond SCORE.

Next, we investigated associations between classical risk factors and CAC and found that hypertension, hypercholesterolemia, and obesity were independently associated with CAC in both sexes in a middle-aged Dutch population. Similar findings have been reported in prior studies.[12,13,27] Furthermore, we observed that current smoking was associated with CAC only in women. Previous studies reported inconsistent findings in this association.[12,28] The fact that we found the association only in women may be because the effect of smoking on developing CAC is time and dose dependent, and it is possible that women are more sensitive to the harmful effect of tobacco than men. Furthermore, the relation between diabetes and CAC was not significant anymore in the fully adjusted model. However, there is an overlap in the 95% CI of the estimated effects between the basic regression model and the fully adjusted model, suggesting that the lack of significance in the fully adjusted model may be owing to the low prevalence of diabetes, resulting in insufficient power.

Only 18.5% of CAC presence in men and 31.4% of CAC presence in women was attributable to classic risk factors. In other words, only a limited proportion of CAC presence would be theoretically reduced by modifying the classic risk factors to healthy levels. No prior studies exist that estimated the PAF of classic risk factors for CAC. However, the PAF of classic risk factors for subclinical coronary atherosclerosis in our study was lower than generally reported for overt CVD.[29–31] This low proportion of CAC presence, attributable to classic risk factors, strengthens the theory that CAC reflects the aggregated effects of exposure to known and unknown risk factors over time on the coronary arterial wall. Efforts to explore unknown amendable risk factors are needed for potential preventive intervention.

This study has some limitations. First, although we estimated the proportion of CAC presence that would be reduced by eliminating the classic risk factors, the causality between risk factors and presence of CAC cannot be established owing to the cross-sectional design. PAF is interpreted under the assumption that classic risk factors lead to aggregated atherosclerosis burden that can be quantified using CAC scoring, rather than the other way around. Second, we included self-reported information about smoking habits, use of medication, and medical history as part of the process to define participants' risk factors. This may be subject to recall bias and may have mitigated the PAF of the risk factors. However, most subjects with hypertension (75%), hypercholesterolemia (87%), and diabetes (70%) were also identified based on blood pressure and laboratory tests that were measured in a standardized fashion as part of the Lifelines procedures (available in 99.95% of the participants). Third, although our study sample was derived from the Lifelines cohort that represents the northern Dutch, primarily White population, generalizability of our result to populations beyond this cohort is unknown. Consequently, external validation of our results will be needed. Fourth, given the nonenhanced cardiac CT for CAC scoring, only calcified plaque could be quantified. Although a small proportion of individuals with a zero CAC score has noncalcified plaque,[32] in general, adverse cardiac event rates in individuals with zero CAC have shown to be exceedingly low.[6]

In conclusion, in this middle-aged cohort, in more than half of men and in a quarter of women CAC was present. One out of 4 men at high risk (SCORE $\geq$5%) could be placed into a lower risk category owing to absence of CAC. Thus, adding CAC scoring to SCORE may have considerable effect on cardiovascular risk classification. A limited proportion of CAC in the middle-aged population could be prevented if exposure to classic risk factors was eliminated.

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