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CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Coronary artery calcium score percentiles: data from a single center in Turkey

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PURPOSE

The coronary artery calcium (CAC) score is used in decision-making for preventive medications in patients with borderline clinical risk scores. Both absolute and percentile CAC scores can be used; however, a percentile CAC score is especially useful in young patients and women. The aim of this study is to present CAC score percentiles across age categories in women and men using a large database.

METHODS

Bilkent City Hospital database was screened for patients who underwent CAC score measurements between January 2021 and March 2022. Of the 4,487 patients, 546 were excluded due to 1) a history of coronary stent implantation or bypass surgery or 2) missing information regarding a history of revascularization or calcium scores. Therefore, the final study population included 3,941 participants. The percentiles for age categories within each sex were tabulated, and percentile plots were created for each sex using locally weighted scatterplot smoothing regression.

RESULTS

The proportion of men included in the study was higher compared with that of women (57.09% vs. 42.91%). The mean age was 52.20 ± 11.11 years, and it was higher in women than in men (54.07 ± 10.47 vs. 50.80 ± 11.37, respectively; $P < 0.001$). A zero CAC score was observed in 2,381 (60.42%) patients; the percentage was higher in women than in men (68.60% vs. 54.27%; $P < 0.001$). When the cut-off value for the high-risk category was taken as the 75th percentile, a non-zero CAC score directly assigned a patient into the high-risk category in women aged <55 years and men aged <45 years. Percentile plots were also provided for each sex.

CONCLUSION

In this large-scale study, including patients referred for CAC scoring and/or coronary computed tomography angiography, CAC score percentiles were provided for women and men across the selected age categories which may be in therapeutic decision-making. As an approximate rule of thumb, a non-zero CAC score corresponds to the high-risk category in women aged <55 years and in men aged <45 years.

KEYWORDS

Coronary artery, calcium score, computed tomography, percentiles, cardiovascular risk scores

The preliminary results of this study were presented (oral presentation) in the National Radiology Congress on November 3, 2022, Antalya, Turkey.

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Cardiovascular (CV) diseases, particularly coronary artery disease, are the leading causes of death worldwide.[1,2] Detection of high-risk individuals is of prime importance for the application of appropriate preventive measures. For this reason, guidelines recommend using clinical risk scores, such as the Framingham risk score or the pooled cohort estimates score for the American population[3] and the SCORE-2 tool for the European population.[4] Despite using these scores, some people may still experience CV events; therefore, other potential risk markers have been evaluated to make a better classification. The coronary artery calcium (CAC) score is independently associated with future risk of coronary events[5,6] and is recommended for use as a risk modifier in patients with a borderline risk category based

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on clinical risk scores. A CAC score can be used in risk estimation as an absolute value or percentile for sex and age categories. The use of absolute scores seems to be a better method than percentiles in risk classification for future CV events.[7] However, percentile scores may especially be useful in young people and women, as the absolute score may be too low to predict future events.[8-11] The American guidelines recommend the cut-off value of the 75^{th} percentile as the risk modifier in patients with a borderline risk score based on the conventional risk score calculation.[3]

CAC score percentiles vary not only among age and sex categories but also among populations.[12,13] These findings suggest the necessity of calculating CAC scores and percentiles for each population. According to the authors' knowledge, there is no high-volume study evaluating the CAC score percentiles in Turkey; hence, it is possible that data from the Multi-ethnic Study of Atherosclerosis (MESA) for the white/Caucasian population are used for this purpose. In this study, the authors aimed to calculate the CAC percentiles for each sex and age categories and to evaluate the absolute values that correspond to the high-risk (75^{th}) percentile. The authors also planned to provide percentile plots of CAC scores for each sex.

Methods

The present study was approved by the Ankara Bilkent City Hospital Institutional Review Board (20.04.2022/E1-22-2563) and was performed according to the Declaration of Helsinki principles. Informed consent was waived, as the study was conducted retrospectively with use of the hospital database.

Main points

- More than half of the study population (60.42%) had zero coronary artery calcium (CAC) scores; the percentage was significantly higher in women than in men (68.60% vs. 54.27%; $P < 0.001$).
- The prevalence of non-zero CAC scores increased with age; the increase was more prominent in men than in women. Of note, a non-zero CAC score developed approximately 10 years earlier in men than in women.
- As an approximate rule of thumb, a non-zero CAC score corresponded to the high-risk category (75^{th} percentile) in women aged <55 years and in men aged <45 years.
- The CAC score percentiles were provided for each sex across the selected age categories.

Study population

The authors of the present study screened for patients who underwent coronary computed tomography (CT) angiography (CTA) and CAC score calculation between January 01, 2021, and March 01, 2022, in the radiology department of Ankara Bilkent City Hospital, Ankara, Turkey. The exclusion criteria were 1) patients with a coronary stent or bypass graft and 2) patients with missing information regarding history of revascularization or calcium scores. Of the 4,487 patients, 546 (12.2%) were excluded; finally, the study population included 3,941 participants. The flowchart for creating the present study population is presented in Figure 1. Among the study population (n = 3.941), 3.910 had received both CAC scoring and CTA, and only 31 patients had received CAC scoring alone.

Risk factors for coronary artery disease were obtained from the hospital database. The study population was divided into age categories: 1) patients aged <40 years; 2) patients with 5-year intervals aged 40–80 years; and 3) patients aged ≥80 years. Next, analyses were conducted for women and men separately.

Coronary computed tomography angiography and coronary artery calcium score calculation

Coronary CTAs and CAC score calculations were performed on a 512-detector CT scanner with dual-energy (General Electric, Revolution CT, GE Healthcare, Wisconsin, USA). A beta-blocker (metoprolol 50–100 mg) was given to patients with a heart rate of >65 bpm at least one hour before coronary CTA according to a cardiologist's recommendation, and an additional dose (up to the total dose of 200 mg) was given if necessary. CT was electrocardiographically triggered at 60%–80% of the R-R interval. Retrospective electrocardiogram (ECG) gating was performed in patients with high heart rates for CTA, and prospective ECG-triggered CT acquisition was used for CAC scoring. Before contrast material injection, non-enhanced images for CAC scoring were obtained. Intravenous iodinated contrast material was injected at a rate of 4–6 mL/sec, followed by saline infusion. The CTA and CAC scan parameters were as follows: 1) 16 cm detector; 2) 100–120 Kv (120 kV for individuals with body mass index of >29, 100 kV for others); 3) 300–720 mA; 4) section thickness of 0.625 mm for CTA and 2.5 mm for CAC score scanning; 5) field of view of 25 cm; 6) rotation time of 0.28 secs; 7) 512 × 512 pixel matrix; and 8) window/level: 550/100.

The CAC was defined as a plaque of at least three contiguous pixels with an attenuation of ≥130 Hounsfield units (Figure 2). The SmartScore 4.0 (General Electric, Revolution CT, GE Healthcare, Wisconsin, US) software system was used for CT image postprocessing, and the CAC score was calculated using the Agatston method.[14]

Statistical analysis

Categorical variables were presented as frequency and percentages, and continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on whether or not they have a normal distribution (with the exception of the CAC score). The CAC score had a skewed distribution but was presented as mean ± SD and median (IQR).

Categorial variables were compared using the chi-squared test. The trend of non-zero CAC scores across the age categories was assessed in women and men separately using the Cochrane-Armitage test. Continuous variables were compared using the t-test if they conformed to the normal distribution and using the Mann–Whitney U test if they did not

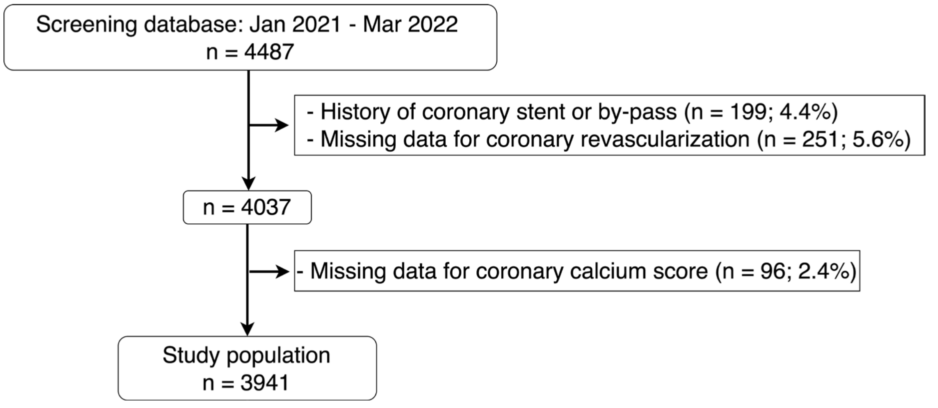

Figure 1. Flowchart for the study population.

conform to the normal distribution. The level of significance (alpha) was set at 0.05.

Percentiles were tabulated across the sex and age strata. Most of the patients had zero CAC scores. In the MESA, investigators proposed a flexible non-parametric model enabling the calculation of CAC percentiles for a particular age (rather than for age categories), while taking the inflated zero values into consideration.[13] In order to be flexible and comparable to the MESA, the authors of the present study followed a similar method. Briefly, locally weighted scatterplot smoothing (LOWESS) regression with a bandwidth of 0.8 was applied to the log-transformed non-zero CAC score values for women and men, separately. The residuals were obtained by subtraction of the predicted value from each log-transformed observation; the residuals were then ranked, and percentiles from 1^{st} to 99^{th} were calculated. Adding these values to the fitted value for each age and sex provided the estimated percentile for the log-transformed non-zero CAC score values. Taking the exponential of the estimated percentiles yielded the k^{th} percentile of non-zero CAC distribution. For the zero CAC proportions (p), which is also calculated with LOWESS regression, the k^{th} percentile was calculated according to the following formula: $100*(p + [(1-p)*k]/100)$. Using this method, the authors of the present study plotted the 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles for women and men. The non-parametric method used a smoothing approach and estimated the percentiles from the shape of the observed CAC score distribution over the whole age range; it also had the advantage of requiring no assumption.[13,15] Analyses were made using Stata, v. 17 (StataCorp, TX, USA).

Results

The proportion of men was higher than that of women (57.09% vs. 42.91%). The mean age was 52.20 ± 11.11 years; the mean age was higher in women than in men (54.07 ± 10.47 vs. 50.80 ± 11.37, respectively; $P < 0.001$). While the proportions of diabetes mellitus and hypertension were significantly higher in women than in men, the smoking rate was lower. Statin use was similar in women and in men (Table 1).

The median value of the total CAC score was zero for women and men, but the values were higher in men than in women (Table 1).

A zero CAC score was observed in 2.381 (60.42%) patients, and the percentage was higher in women than in men (68.60% vs. 54.27%; $P < 0.001$). The distributions of CAC score categories over the age categories for each sex are presented in Figure 3. There was a significant decrease in patients with a zero CAC score across the age categories ($P < 0.001$), and the trend was more prominent in men than in women (the results of the chi-squared test and the P values for the non-linear were 26.7 and $P < 0.001$, respectively, in men; and 17.8 and $P = 0.013$, respectively, in women, Figure 3).

The percentiles of CAC scores over the age categories are presented in Table 2. The median CAC score (50^{th} percentile) was zero for the age categories of <65 years in women and <55 years in men (Table 2); this suggests that at least half of women aged <65 years and men aged <55 years have a zero CAC score. This finding also indicates that a

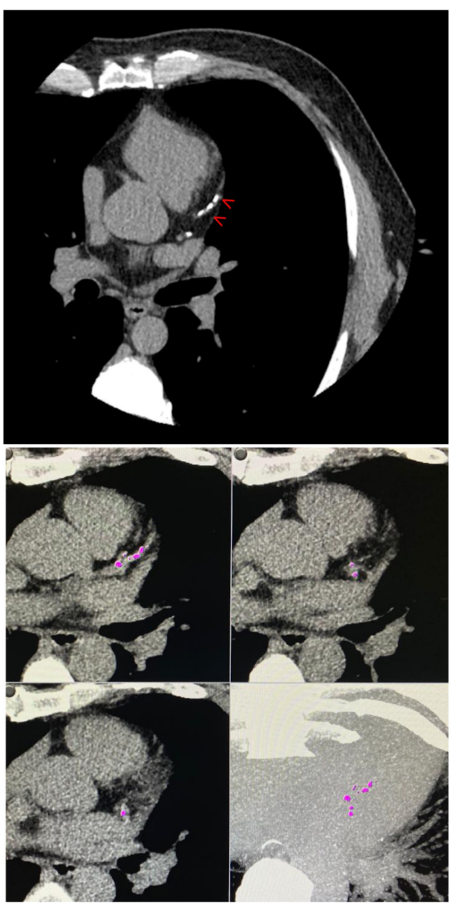

Figure 2. Calcified plaques in the coronary artery territory (arrows in the upper panel) and the postprocess of CAC score calculation with SmartScore (lower panels). CAC, coronary artery calcium.

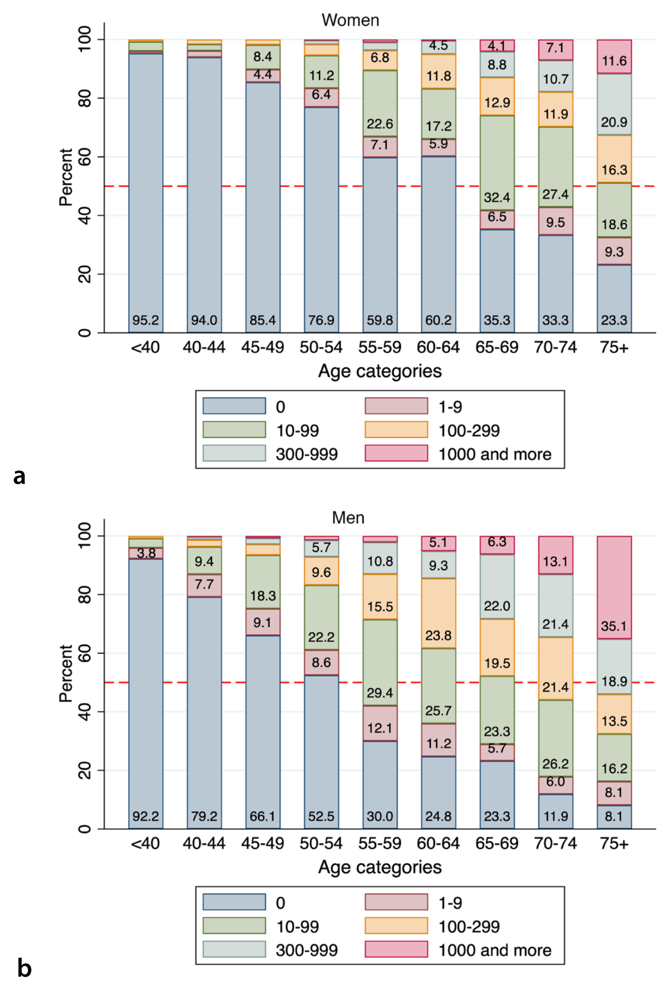

Figure 3. (a, b) Coronary artery calcium score categories across the age categories in women (**upper panel**) and in men (**lower panel**). Some of the percentages with <4% were not shown for clarity of the figures.

10-year gap exists between women and men for the median CAC score to remain at zero.

In women aged <40 years, the 95th percentile of the CAC score was zero, meaning that a zero CAC score is expected in at least 95% of the women in this age group (Table 2). A non-zero CAC score puts a woman into the 95th percentile in the age category of 40–44 years and higher than the 75th percentile in the age categories of 45–49 and 50–54 years (Table 2). Therefore, when the cut-off value for the high-risk category is taken as the 75th percentile,[3] a non-zero CAC score directly puts a woman into the high-risk category under the age categories of <55 years. On the other hand, in men, a non-zero CAC score corresponds to a >90th percentile for the age category of <40 years, and a >75th percentile for the age category of 40–44 years. Therefore, for the cut-off value of the ≥75th percentile, a non-zero CAC score directly puts a man into the high-risk category if he is in the age category of <45 years. This finding also indicates that a 10-year difference exists between women and men in terms of being in the high-risk group.

For each age, rather than the age categories, the 25th, 50th, 75th, and 90th percentiles of CAC scores are plotted in Figure 4.

Discussion

This study demonstrated that more than half of the included women and men had zero CAC scores. Also, the increase in the percentage of non-zero CAC scores with age is more prominent in the earlier ages (approximately 10 years earlier) in men than in women; furthermore, non-zero calcium approximately corresponds to the high risk [75th percentile according to the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines] group in women aged <55 years and in men aged <45 years.

Coronary artery disease is one of the leading causes of mortality and morbidity in developing countries. Preventive strategies regarding starting or intensifying preventive medications, particularly statins, are based on the individual risk of future CV events, which is usually calculated with clinical risk scores, such as Framingham, pooled cohort estimates, or SCORE-2 tools.[3,10] To make a better risk stratification, non-traditional risk modifiers, such as a CAC score and carotid ultrasonography, have been recommended in patients with low to moderate risk for whom the decision for treatment is uncertain or at the threshold level.[3,10,16]

Table 1. Characteristics of the study population

	Women	Men	Total	*P* value
n (%)	1691 (42.91)	2250 (57.09)	3941 (100.00)	
Age, mean ± SD	54.07 ± 10.47	50.80 ± 11.37	52.20 ± 11.11	<0.001
Diabetes mellitus, n (%)*	399 (23.81)	346 (15.57)	745 (19.11)	<0.001
Hypertension, n (%)*	701 (41.83)	652 (29.37)	1353 (34.73)	<0.001
Smoking, n (%)*	293 (19.42)	651 (32.80)	944 (27.02)	<0.001
Statin use, n (%)*	210 (12.57)	282 (12.69)	492 (12.64)	0.908
CAC score, mean ± SD	59.31 ± 254.16	106.79 ± 372.26	86.4 ± 327.66	<0.001
CAC score, median (IQR)	0.00 (0.00; 11.00)	0.00 (0.00; 50.00)	0.00 (0.00; 32.00)	<0.001
CAC score categories				
Zero	1160 (68.60)	1221 (54.27)	2381 (60.42)	<0.001
1-9	93 (5.50)	186 (8.27)	279 (7.08)	
10-99	255 (15.08)	414 (18.40)	669 (16.98)	
100-299	105 (6.21)	218 (9.69)	323 (8.20)	
300-999	55 (3.25)	149 (6.62)	204 (5.18)	
1000 or more	23 (1.36)	62 (2.76)	85 (2.16)	

*The denominator is slightly different due to some missing values; CAC, coronary artery calcium; IQR, interquartile range (Q1-Q3); SD, standard deviation.

Table 2. Coronary artery calcium score percentiles across the age categories in women (A) and in men (B)

A. Women

	Percentiles							
Age	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**n**
<40	0	0	0	0	0	0	0	126
40-44	0	0	0	0	0	0	1	182
45-49	0	0	0	0	0	11	25	274
50-54	0	0	0	0	0	43	119	295
55-59	0	0	0	0	27.5	109	170	296
60-64	0	0	0	0	42	180	281	221
65-69	0	0	0	28	104	361	578	170
70-74	0	0	0	22	148	700	1405	84
75-79	0	0	0	70	439.5	813	1330	36
80+	6	6	50	853	1628	2742	2742	7

B. Men

	Percentiles							
Age	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**n**
<40	0	0	0	0	0	0	9	346
40-44	0	0	0	0	0	28	88	298
45-49	0	0	0	0	9	56	127	383
50-54	0	0	0	0	50	200	385	406
55-59	0	0	0	20	130	400	600	323
60-64	0	0	1	34	179	432	1095	214
65-69	0	0	1	81	313	701	1080	159
70-74	0	0	14.5	114.5	443	1187	2218	84
75-79	0	5	38	215	1176	1795	4002	31
80+	153	153	422	643.5	1308	2656	2656	6

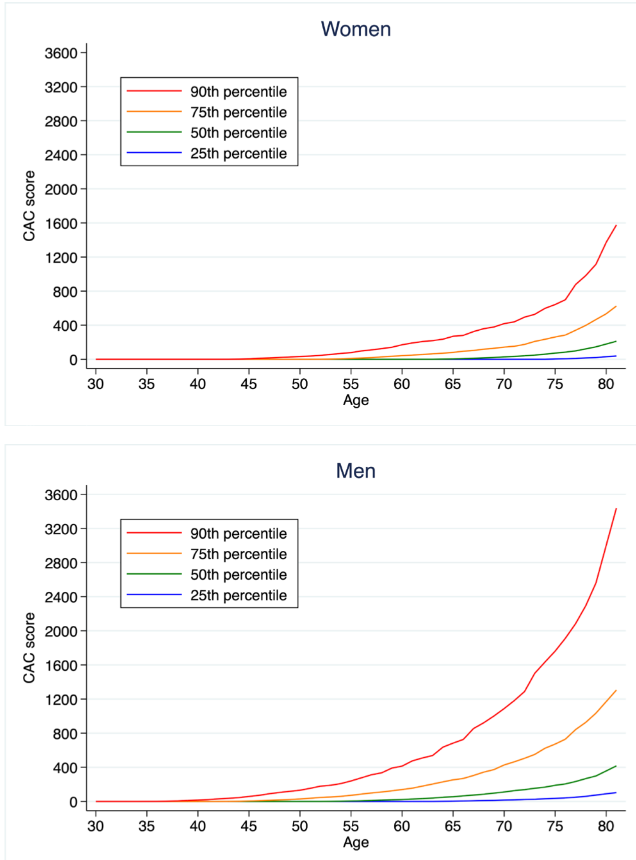

Figure 4. (a, b) Percentile plots for CAC scores in women and men. CAC, coronary artery calcium.

A CAC score is usually used either as an absolute or percentile value. In the MESA, the absolute score was found to be more predictive than the percentile score in predicting CV outcomes.[7] However, percentile scores are preferable in young patients and women, as the absolute CAC score has low specificity in the risk reclassification in these patients due to the low probability of calcium in the atherosclerotic plaques.[9-11] The ESC prevention guidelines recommend comparing the CAC score with the values expected for a patient of the same age and sex.[10] The ACC/AHA prevention guidelines use the cut-off value of ≥100 Agatston units or the 75th percentile to determine the high-risk group among patients with moderate risk or selected borderline risk according to the clinical risk scores.[3]

The authors of the present study found that 68.6% of women and 54.3% of men had zero CAC scores. The proportion of zero CAC scores differs between studies. For example, the proportion is 49% in the CAC consortium,[11] 36% in women and 17% in men in the ELSA-Brasil study,[12] and 62% in women and 40% in men in the MESA.[13] These differences may be explained by the differences between the population characteristics, ethnicity, and age. The authors of the present study also observed that the mean CAC scores were lower than the values for the white population in the MESA (59 vs. 96 for women and 106 vs. 298 for men).[17] The major factor for these differences is that the white population in the MESA is, on average, 11 years older than that in the present study population. However, its effect on the interpretation of the results is probably negligible, as both studies present age-category-specific percentile values and plot the percentiles across ages rather than giving overall mean values alone. As expected, both studies showed that an increase in the CAC score with age is more prominent in men than in women.

Men usually develop CV diseases approximately 9–10 years earlier than women.[18] The CAC consortium study showed that a 75% prevalence of a non-zero CAC score was observed nine years earlier in men than in women.[11] As expected, the present study shows that the percentage of patients with zero CAC score decreases significantly with age and that the decrease is more noticeable in men than in women. Moreover, when the cut-off value of percentiles for the definition of the high-risk group is taken as the 75th percentile, a non-zero CAC score corresponds to the high-risk group for the age categories of <55 years in women and <45 years in men. This finding simplifies the categorization of patients, especially for busy clinicians, when using a treatment decision for a given patient with a borderline risk group based on the conventional risk scores. Similarly to the present findings, in the white ethnicity subset of the MESA, the CAC score for the 75th percentile was zero for the age categories of women aged <55 years.[13] The MESA included participants between the ages of 45 and 84; therefore, no information for men aged <45 years was provided. Thus, no comparison could be made with the present results. In another analysis of the MESA, non-zero CAC was found to be a >75th percentile marker in women aged <60 years and in men aged <50 years in the overall population.[19] Although the age limits are slightly different, the results are consistent with the present findings as well as with previous studies regarding a ~10-year gap of protection between women and men.[11,18] It should be noted that these simplifications are based on age categories rather than on a particular age. More reliable risk estimation for each age can be obtained using the percentile plots for a certain age.

An overexpression of zero CAC values in the dataset may affect choosing statistical approaches. The traditional approach in calculating percentiles is to calculate the percentiles across each age category (Table 2).[20] On the other hand, the MESA investigators used a different approach that has several advantages to the conventional method, such as the flexibility of calculating percentiles for a particular age rather than age categories, considering the overexpression of zero values, and requiring no statistical assumption.[13,15] In the present study, the percentiles were plotted by applying the method used in the MESA, letting the authors take advantage of this method and ensuring that the results would be comparable with other studies.

The percentiles may vary depending on the population. To the authors' current knowledge, centers providing CAC score percentiles in their reports in Turkey are probably using the data from the MESA for the white/Caucasian population due to a lack of data obtained from Turkey. The present study provides local data that may be used in treatment decisions for preventive measures, particularly statin treatment, in patients in the borderline risk category (according to the guidelines' recommendation).

A considerable number of patients undergoing coronary CTA have non-significant atherosclerotic plaques. The Scottish CT of the HEART study demonstrated that lesion severity, CV risk score, CAC score, and plaque characteristics were all important factors for future CV events in univariable analyses.[21] However, in the multivariable analysis, only the CAC score was found to be an independent risk factor for CV events. These findings suggest that the risk is dominated by CAC; this is probably due to being a surrogate marker of an atherosclerotic plaque burden. Therefore, the present data might also be useful in decision-making for statin treatment in patients with non-significant coronary plaques on coronary CTA, as it provides overall information for atherosclerotic plaque burdens.

The present study has both its strengths and its limitations. First, the data comes from a single center; hence, it cannot be said that the data is truly representative of the Turkish population. However, Bilkent City Hospital is one of the biggest hospitals in Turkey and admits patients from a diverse geographical population; this may, at least partially, reduce the negative impact on result generalizability. Second, CAC score calculation is appropriate and useful for patients without "known" significant coronary artery stenosis at the baseline. As the data was obtained from the hospital records, the history of coronary artery disease at the baseline could not be obtained in all patients. However, patients with a stent or bypass graft were excluded from the study. On the other hand, the study authors do not consider this an issue of major concern, as most patients with severe coronary artery disease undergo stenting or coronary bypass surgery, and patients with typical symptoms suggesting severe coronary artery disease are appropriately referred to conventional angiography rather than coronary CTA. Third, due to the retrospective nature of the study, there is no reliable information available on the symptom status. The present study's population includes a referral population that underwent mostly CAC scoring and coronary CTA, making it more suitable for application of the study results. Considering the cost and difficulty of conducting a large prospective study, the present study provides acceptable results until such a prospective study is conducted and published. Fourth, the present data were obtained retrospectively from the hospital CT reports; therefore, the intra-observer and interobserver agreement of CAC score measurements was not assessed. However, the study authors think that this might not be a major issue, as CAC scoring is well-standardized, and the images are interpreted by dedicated and experienced radiologists at the Bilkent City Hospital. Fifth, this study provides cross-sectional data for CAC score percentiles in women and men across age groups. As in similar studies, the patient's lifestyle, medications, and environmental factors were not taken into consideration for percentile calculation. As these factors are important potential confounding factors, they should be included in studies that evaluate (or create) a prediction model for future events. The present study provides only snapshot information for the study population but does not provide a prediction model. On the other hand, it provides information for a non-zero CAC score that corresponds to the guidelines-recommended cut-off value for the high-risk category (75th percentiles).

In conclusion, this study provides CAC score percentiles for sex and age categories from 3,941 participants referred for CAC scoring and/or coronary CTA; it also demonstrates that more than half of the study population have zero CAC scores. Also, a non-zero CAC score develops approximately 10 years earlier in men than in women, and a non-zero CAC score is assigned to the high-risk category (75th percentile) in women aged <55 years and in men aged <45 years.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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