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Research paper

A pooled-analysis of age and sex based coronary artery calcium scores percentiles

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ABSTRACT

Background: Age and sex based coronary artery calcium score (CAC) percentiles have been used to improve coronary artery disease (CAD) risk prediction. However, the main limitation of the CACs percentiles currently in use is that they are often based on single studies. We performed a pooled analysis of all available studies that reported on CAC percentiles, in order to develop more generalizable age and sex nomograms.
Methods: PubMed/Medline and Embase were searched for studies that reported nomograms of age and sex-based CACs percentiles. Studies were included if they reported data collected among asymptomatic individuals without a history of cardiovascular disease. Absolute CACs for each specific percentile stratum were pooled and new percentiles were generated taking into account the sample size of the study.
Results: We found 831 studies, of which 12 met the inclusion criteria. Data on CACs percentiles of 134,336 Western and 33,488 Asians were pooled separately, rendering a weighted CACs percentile nomogram available at https://www.calciumscorecalculator.com. Our weighted percentiles differed by up to 24% from the nomograms in use today.
Conclusions: Our pooled age and sex based CACs percentiles based on over 155,000 individuals should provide a measure of risk that is more applicable to a wider population than the ones currently in use and hopefully will lead to better risk assessment and treatment decisions.

1. Introduction

Accurate risk prediction is of seminal importance for primary prevention of coronary artery disease (CAD). Currently risk assessment relies on risk factor-based algorithms such as the ACC/AHA or SCORE calculators.[1,2] Unfortunately, these risk models are not completely accurate, and several individuals are misclassified.[3,4] Hence, the addition of coronary artery calcium (CAC) scoring to risk factors based prediction models has been proposed to improve risk assessment.[5]

Several prospective studies have shown that CAC predicts CAD events independent of other risk factors, and better than other markers such as carotid intima media thickness or arterial stiffness.[5]

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List of abbreviations

CAD	Coronary artery disease
CAC	Coronary artery calcification
MESA	The Multi-Ethnic Study of Atherosclerosis
CT	Computed Tomography
USA	United States of America

Additionally, CAC scoring results in a net reclassification improvement of 14–30% over models based solely on traditional risk factors.[3,4] As a results, both European and American guidelines support the use of CAC imaging to refine risk assessment especially in patients at intermediate risk.[6]

However, most patients below 50–55 years of age and especially women will almost never fall into the intermediate risk category. This may cause under estimation of risk and refrainment of treatment, whereas adding CAC imaging could lead to potentially improved outcomes.[7]

Both the absolute and percentile CAC score have been proposed to assess risk although some investigators suggested that the absolute CAC score outperforms the percentiles.[8] However, the absolute CAC score is unlikely to be sufficiently high in young individuals or women to warrant treatment. Therefore, age and sex based percentiles may provide a better insight into a person's atherosclerotic burden in comparison to her/his peers. The two calculators most frequently referred to, the MESA,[9] or Raggi et al.,[10] do not provide data on young individuals (< 45 years of age) and have only limited data on women. Additionally, these two nomograms included data exclusively from individuals living in the USA, therefore the generalizability to other parts of the world such as Europe or Asia is potentially limited.

We aimed to produce nomograms with greater applicability to younger individuals, women and residents of countries outside the USA and especially Asian individuals. Therefore, we performed a pooled-analysis of all studies that reported information on absolute and percentiles of CAC scores.

2. Methods

2.1. Search

We searched Medline/PubMed and Embase for studies reporting on CAC scores in a population of asymptomatic individuals without a history of cardiovascular disease. The studies included individuals randomly selected from the population or individuals who voluntarily underwent cardiovascular risk assessment. Additional studies were included by discussion with the original authors and screening the references of studies selected for inclusion. Only studies that reported on CAC score nomograms with CAC score percentiles in separate age and sex strata were included. The studies included in this meta-analysis reported calcium scores mainly, but not exclusively, acquired with electron beam computed tomography (EBCT) and early generation multidetector CT-scanners. Studies were excluded if the population consisted of a specific risk group (e.g. familial hypercholesterolemia or diabetes mellitus).

Details on the search strategy can be found in the supplemental material available online. The final search was performed on May 8th, 2019. Titles and abstracts were independently screened for potential eligibility by two investigators (M.d.R. and M.Bi.). Subsequently, the investigators assessed the full text of all potentially eligible studies to search for CAC score nomograms as described above. In case of disagreement, a third investigator (S.J.P) was consulted to reach a consensus decision. This study was conducted in line with the PRISMA statement.[11]

2.2. Data extraction

All included studies, published data on CAC score nomograms. From the published nomograms, we extracted the absolute CAC score for each study and each age percentile group. This information was gathered in a pre-specified data extraction table as shown in Supplemental Table S1. To receive permission to use the data and to obtain missing information, 15 authors were contacted. Thirteen authors provided additional information to complete the full nomogram according to the requirements pre-specified in our data extraction table. Five authors provided additional information on age categories not reported in their original publication, whereas eight authors lacked data on the age categories 40–45 and < 40, and could only provide data on the age category < 45. The data from the MESA[9] study, the study by Hopkins et al.[12] and the study by Park et al.[13] were not included in our analyses since the authors of these studies did not provide additional information on 5-year age strata. Because their nomograms were built with 10-year age strata, they are not compatible with our analyses and therefore their nomograms could not be used for this study. For the exception of the data on < 40 years of age by Park et al. which was used for the Asian analysis. Since this only lead to a loss of 5% of the data, we believe that the exclusion of this data will not influence our results.

This analysis was undertaken to create more precise percentiles than the ones currently in use from single studies, such as MESA[9] and Raggi et al..[10] Searching the literature we discovered that a sizeable amount of data was available on Asians alone, and decided to separate this group from the rest, especially since CAC scores in Asians are known to be substantially lower than for other populations. The Asian population consisted mainly of Korean individuals (92%), with a small contribution from Japan (5%) and the USA (3%). No South Asian populations were included. As far as the western populations are concerned, we felt

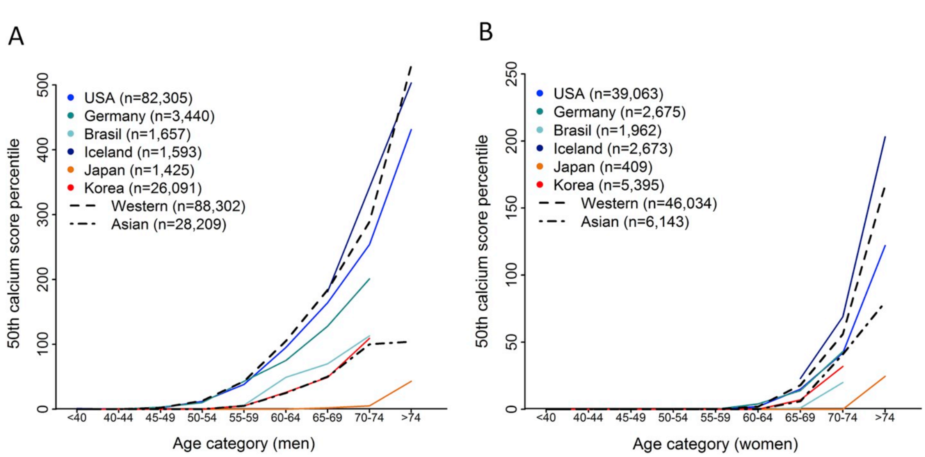

Fig. 1. Median calcium score percentile for individuals from North and South America (the USA and Brazil), Europe (Germany and Iceland) and Asia (Korea and Japan). The dashed lines show the pooled median calcium score percentile for either all Western or all Asian individuals. Note that amount of the combined Western or combined Asian is not the same as the sum of the different countries, since the study by Budoff et al.[14] counts as a whole for the USA and was split into Western and Asian individuals when the pooled nomograms where created.

Table 1
Type of computed tomography scanner and clinical details of the patients included in the analyses as presented by each respective author.

A. Western population

Studies	n	Age mean ± SD	Men n (%)	Race	Country	CT-scan	CT-scan vendor	HT n (%)	Hchol n (%)	DM n (%)	Smoking n (%)	FHx n (%)	BMI mean ± SD
Raggi 2000[10]	10,989	NR	6070 (55)	Mixed	USA	Imatron C100 (EBCT)	Imatron (South San Francisco)	4572 (47)	5448 (56)	1070 (11)	4183 (43)	6712 (69)	NR
Hoff 2001[16]	35,246	51 ± NR	25,251 (72)	Mixed	USA	Imatron (EBCT)	Imatron (South San Francisco)	7049 (20)	12,689 (36)	1057 (3)	5287 (15)	21,853 (62)	NR
Schmermund 2002[20]	1840	56 ± 10	1.413 (75)	White	Germany	Mx-8000 4-S (multidetector)	Philips (Cleveland, Ohio)	820 (42)	1046 (57)	119 (6)	433 (22)	861 (45)	26.2 ± 3.8
Schmermund 2006[21]	4275	59 ± 8	2027 (47)	White	Germany	Imatron C150 (EBCT)	Imatron (South San Francisco)	2351 (55)	2209 (47)	256 (6)	983 (23)	NR	28.0 ± 5.0
Nasir 2004[18]	12,935	53 ± 10	8.720 (67)	Mixed	USA	Imatron C150 (EBCT)	Imatron (South San Francisco)	2717 (21)	3363 (26)	647 (5)	1423 (11)	5951 (46)	NR
Mitchell 2001[17]	17,678	NR	11.062 (63)	Mixed	USA	Imatron C150 (EBCT)	Imatron (South San Francisco)	NR	NR	NR	NR	NR	NR
Pereira 2016[19]	3619	50 ± 8	1657 (46)	Mixed	Brazil	64 detector (multidetector)	Philips (Best, Netherlands)	517 (23)	1575 (69)	–	323 (14)	NR	NR
Budoff* 2007[14]	23,700	56 ± 11	16,748 (71)	Mixed	USA	Imatron C150XL (EBCT)	Imatron (South San Francisco)	NR (15)	NR (18)	NR (4)	NR (9)	NR (58)	NR
Wong 2002[22]	19,788	NR	13,761 (70)	Mixed	USA	Imatron C100 (EBCT)	Imatron (South San Francisco)	NR	NR	NR	NR	NR	NR
Gudmundsson 2012[15]	4266	76.5 ± 5.5	1593 (37)	White	Iceland	Siemens 4 (multidetector)	Siemens (Erlangen, Germany)	3324 (63.8)	1193 (22.9)	620 (11.9)	639 (12.3)	1875 (36)	27.0 ± 4.4
Total	134,336	–	88,302 (66)	–		–	–	–	–	–	–	–	–
Asian population													
Budoff* 2007[14]	1032	56 ± 11	693 (67)	Asian	USA	Imatron 150XL (EBCT)	Imatron (South San Francisco)	(15)	(18)	(4)	(9)	(58)	NR
Ohmoto 2016[24]	1834	56 ± 10.9	1425 (78)	Asian	Japan	Acquilion 64 multidetector	Toshiba (Tochigi, Japan)	480 (26)	946 (52)	195 (11)	590 (32)	NR	23.4 ± 3.2
Yang 2016[23]	31,066	53.8 ± 8.5	25,798 (83)	Asian	Korea	NR	General Electric MS (Milwaukee, USA)	11,643 (37)	14,064 (45)	3648 (12)	7958 (25)	NR	24.5 ± NR
Total	34,352[#]	–	28,209[#] (82)	–		–	–	–	–	–	–	–	

Continuous data are expressed as mean ± SD, categorical data as absolute number with (percentages). BMI = Body Mass Index; CAD = coronary artery disease; DM = diabetes mellitus; FHx = positive family history; Hchol. = hypercholesterolemia; HT = hypertension; n = number; NR = not reported; SD = standard deviation. *study appears twice, taking into account Western and Asian individuals separately. [#]including individuals < 40 years, from the study by Park et al.[14]

that we could combine data in a single calculator given the small proportion of non-Whites in North American and especially European populations. This was also necessary because in most studies from the USA a clear definition of race and ethnicity was not reported, and some racial mixing is expected to have occurred. The western populations comprised individuals from the USA (89%), Brazil (2%), and Europe (9% in total with 5% from Germany and 4% from Iceland). To assess whether there were large differences between countries, we compared the absolute calcium scores of the median percentile according to various age groups, per country and found that these were very similar for the USA and Europe (Fig. 1). We therefore pooled these two populations to create percentiles for a Western population. The only countries that deviated from the rest were Brazil and Japan, which is most likely due to their small sample size.

2.3. Statistical analysis

Data extracted from the nomograms were used in the analyses. We analyzed the data separately for Western and Asian individuals and first created subgroups of the same age and sex. Then, from each study we selected the absolute CAC score of a certain percentile and calculated the average absolute CAC score for either Western or Asians individuals separately within this specific percentile. For example, in the study by Raggi et al.[10] the 50th CAC score percentile for a 45–49 year old man is 3. All absolute CAC scores from all other studies within the same age, sex and percentile group were then averaged, taking into account the sample size of each study, using the following calculation:

Table 2
Pooled nomograms of absolute CAC scores and corresponding percentiles for each age category in Western and Asian men and women.

A. Western men

	Age	< 40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	> 74
Percentile	**n**	6708	11886	15263	16563	13134	8987	5677	3169	1882
	10th	0	0	0	0	0	0	0	0	2
	25th	0	0	0	0	2	9	24	48	109
	50th	1	0	2	11	38	94	163	254	434
	75th	2	8	32	92	198	381	569	781	1123
	90th	14	51	141	291	538	851	1139	1493	1934
	95th	42	114	280	586	966	1341	1794	2428	2799

B. Western women

	Age	< 40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	> 74
Percentile	**n**	2689	3945	6401	8348	7089	5073	3451	2271	1419
	10th	0	0	0	0	0	0	0	0	0
	25th	0	0	0	0	0	0	0	2	13
	50th	0	0	0	0	0	2	15	42	121
	75th	0	0	1	4	20	57	123	210	419
	90th	2	5	20	51	126	199	352	544	911
	95th	6	17	55	98	236	448	598	952	1633

C. Asian men

	Age	< 40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	> 74
Percentile	**n**	1520	2952	6129	8557	5386	4034	1677	993	90
	10th	0	0	0	0	0	0	0	0	0
	25th	0	0	0	0	0	0	2	16	1
	50th	0	0	0	0	5	25	50	100	104
	75th	0	0	3	23	63	124	215	321	464
	90th	1	17	49	121	221	352	537	681	807
	95th	5	59	117	228	410	586	796	936	1195

D. Asian women

	Age	< 40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	> 74
Percentile	**n**	256	695	792	2261	1412	1416	577	383	42
	10th	0	0	0	0	0	0	0	0	11
	25th	0	0	0	0	0	0	0	0	52
	50th	0	0	0	0	0	0	6	41	80
	75th	0	0	0	0	3	23	98	146	150
	90th	0	3	1	12	50	96	311	409	236
	95th	0	4	6	42	112	183	514	476	150

Pooled absolute CAC score of percentile

$$x = \sum \left(\frac{study\ participants_i}{total\ participants} \times CAC\ score_i\right)$$

where (i) is the study number (i.e. study 1, study 2, etc.). As a result, we created a pooled estimate of the absolute CAC score for a given percentile creating a new weighted nomogram. We then designed a new calculator by plotting the 10th, 25th, 50th, 75th, 90th and 95th percentile against the absolute CAC score in each age, sex and race category and connected the data points with a line. These 6 percentile levels were used to provide interpolated estimates for each age and sex stratum for either Western or Asian individuals. All analyses were performed using SPSS for Windows 23.0 and statistical environment R Studio 0.99.903 (R foundation for Statistical Computing Vienna, Austria). Since we did not have individual data, we weren't able to test whether there were statistically significant differences between percentile curves of either Asian or Western individuals.

This research was exempt from review by an ethical review board because it involved solely a mathematical reanalysis of data previously published and no individual patient data was utilized.

3. Results

3.1. Search and selection

The search rendered a total of 831 hits, of which 593 did not fulfill the inclusion criteria; we were left with 241 studies potentially eligible after screening their titles and abstracts (Supplemental Fig. 1). Among these, 12 studies fulfilled the inclusion criteria and contained all information necessary to create the new CAC score nomogram and were therefore included in this analysis.[10,14–24] The reasons for exclusion of potentially eligible studies are provided in Supplemental Fig. 1.

3.2. Characteristics of the studies included in the analyses

The characteristics of the studies included in our analyses are provided in Table 1. In total, we utilized age- and gender-specific CAC score percentile nomograms derived from 12 studies, of which 9 reported solely on Western populations, 2 solely on Asians and 1 study, the study by Budoff et al.[14] reported on both Western and Asian individuals. A total of 134,336 asymptomatic patients from the western hemisphere were included,[10,14–22] of which 34% were women and 19% were under the age of 45 years. In the analyses of Asians, a total of 33,488 asymptomatic individuals were included,[13,14,23,24] of which 18% were women and 12% were under the age of 45 years.

3.3. Pooled-analysis of CAC score nomograms

The CAC score percentile nomograms of each individual study included in the analyses are shown in Supplemental Tables S1(a–d). The total number of individuals in each age category for Western men and women and Asian men and women, can be found in Supplemental Table S2.

Fig. 1 shows the median calcium score percentile for individual countries and the combined data for either the Western or Asian populations.

The weighted average absolute CAC score and the corresponding percentile per age and sex for Asian and Western subjects are presented in Table 2 and Fig. 2.

For any given CAC score, the age and sex specific percentile was calculated using the graphs in Supplemental Fig. 2. The average scores were then converted into a calculator which is available online (https://www.calciumscorecalculator.com).

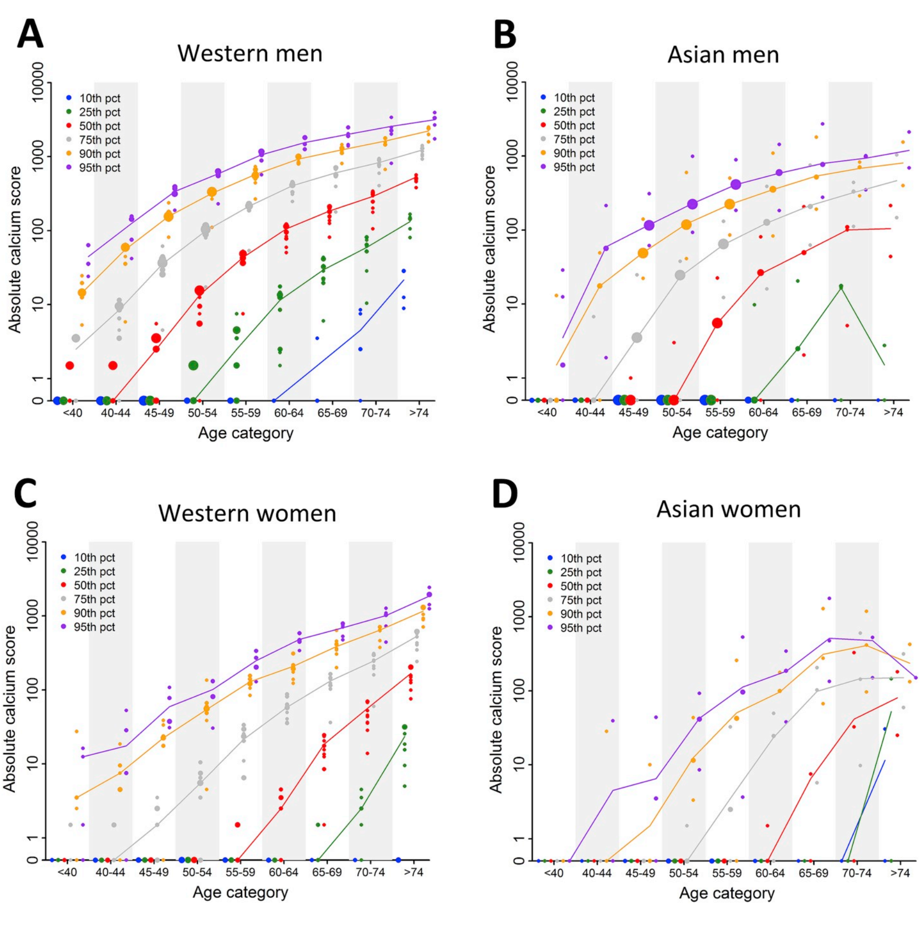

Fig. 2. Agatston CAC score for age and sex based percentiles of all individual studies by age category of A) Western men B) Asian men C) Western women and D) Asian women. Dots represent the Agatston score for a given age and sex percentile (blue = 10th percentile; green = 25th percentile; red = 50th percentile; grey = 75th percentile, orange = 90th percentile; purple = 95th percentile). Each dot represents the coronary artery calcium score percentile from a particular study. The dot size represents the sample size, with larger dots representing larger sample sizes. Lines represent the pooled calcium score percentiles. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.4. Comparison of the pooled age and sex based CAC score percentiles with the currently used nomograms

We compared our nomograms with the only two available, frequently used algorithms by McClelland et al. (MESA study)) and the nomogram by Raggi et al..[9,10] The MESA study included 41% Caucasians, 12% Asians, 26% Blacks and 21% Hispanics. The study by Raggi et al. provided no information on race or ethnicity. The MESA calculator produced age and sex based percentiles up to 24 percentile points higher when compared to our calculator (Table 3). However, percentiles estimated using the tables published by Raggi et al.[10] were consistent with our pooled data calculator. When comparing the nomograms by Raggi et al.[10] and MESA[9], it shows that they are also discordant in some age strata. Unfortunately, the publication by Raggi et al.[10] does not provide exact age and sex based percentiles, but only a median value for each age group.

4. Discussion

In the current study, age and sex CAC score percentiles of 167,824 asymptomatic individuals from different countries were pooled to obtain more universal estimates of percentiles than can be obtained from a single centre or country. We showed that our pooled age and sex percentiles differ substantially from those produced by the MESA investigators and most commonly used in current clinical practice. CAC score percentiles based on relatively small studies are prone to bias, since outliers will add much more to the outcome of small studies than to studies with a large sample size. Consequently, a pooled analysis makes it possible to substantially increase the precision of nomogram calculation. With the large sample size we collected we were able to generate percentiles for groups that are normally underrepresented in single studies, such as the young, the elderly and women. In our analyses there were 11,177 individuals below 40 years of age, 5883 individuals older than 74 years of age and 52,177 women, whereas in MESA[9] the number of individuals in these categories was; 0 young individuals, 174 elderly and 1308 women. In the publication by Raggi et al.[10] the corresponding numbers were; 767 young individuals, 0 elderly and 4295 women. Therefore, the percentiles for these underrepresented groups are likely to be much more accurate in our pooled analyses. In addition, we were also able to produce CAC score percentiles for Asian subjects that have been underrepresented in most studies. To be able to further increase accuracy, one would need the individual CAC scores, which we were unfortunately not able to acquire. Nevertheless, this study provides a nomogram that is likely to be more precise than the nomograms currently in use in clinical practice. To be able to make uniform treatment decisions, based on cut-off values above the 75th percentile, as advised in the AHA/ACC 2018 guidelines,[25] accurate age and sex percentile nomograms are needed. We believe that our calculator may be a more accurate risk assessment tool than the ones currently in use. Nonetheless, Blacks, Hispanics and Chinese populations may be better served by specific nomograms that are currently only available in the MESA calculator, although the number of individuals in each group was limited and therefore prone to error.

4.1. Strengths and limitations

An important limitation of our analyses is that we pooled studies from multiple sites in the world (USA, Europe and South America on the one hand and Korean and Japan on the other). One could argue that this may lead to inaccurate estimates due to the mixing of different races and ethnicities. However, the fact that the median absolute scores for North American and Europeans were very similar is somewhat reassuring. In the ideal world, it would be preferable to obtain separate percentiles for Whites, Blacks, Hispanics, South Asians and East Asians based on large individual data sets. Unfortunately we were unable to obtain the raw data and for many studies it was not possible to discern the racial and ethnic background from the published material. On the other hand, this study does not claim to provide the most accurate age and sex based percentiles possible, but simply aims to generate a calculator that provides more universally usable percentiles. In fact, the percentile calculators most frequently used anywhere in the world today, are derived from nomograms of white American subjects, with only a small percentage of other races.

The majority of studies included in our pooled analysis comprised self-referred or physician referred asymptomatic individuals, as opposed to subjects from the general population. This has likely led to the calculation of higher CAC scores than what would have been derived by scanning a random sample of an unselected population. However, in real life these are the patients most often submitted to CAC screening and our data may be most useful in this setting.

Another limitation worth mentioning is that we pooled data obtained from scanning patients with CT scanners made by different vendors. Most of the data in the studies included in our analyses are based on the reference standard EBCT with fewer studies conducted using MDCT technology. Calcium scores might be underestimated by MDCT,[26] and particularly in obese patients.[27] However, other studies have shown that CAC scores are comparable between EBCT and MDCT[28–31] and for that matter the MESA calculator combined the CAC scores derived with both types of scanners.[32]

Finally, we had to exclude 3 studies, the MESA, the study by Hopkins et al. and the study by Park et al.,[9,12,13] since they used 10-year age strata instead of 5-year strata as we did. We choose not to analyze our data in 10-year strata because CAC scores are not normally

Table 3
Percentiles difference for specific absolute calcium score cut-offs between our pooled analysis and currently used individual studies.

		40			50			60			70		
Sex	Abs CACs	Raggi	MESA	Pooled	Raggi	MESA	Pooled	Raggi	MESA	Pooled	Raggi	MESA	Pooled
Men	10	50–75	–	76	25–50	68	44	10–25	39	24	10–25	19	12
	100	90–95	–	93	50–75	89	75	25–50	68	49	25–50	43	29
	400	95–100	–	100	90–95	98	92	50–75	88	75	50–75	68	55
	1000	95–100	–	100	95–100	99	100	90–95	96	91	75–90	85	78
Women	10	90–95	–	92	75	90	77	50–75	71	69	25–50	47	29
	100	95–100	–	100	90–95	98	95	75–90	89	95	50–75	72	56
	400	95–100	–	100	95–100	99	100	90–95	97	100	75–90	90	81
	1000	95–100	–	100	95–100	99	100	95–100	99	100	95–100	97	95

The age and sex based percentiles of two frequently used algorithms (Raggi et al.[10] and McClelland et al.[9] (MESA study)) and our pooled analysis, for a patient with an absolute CAC score of 10, 100, 400 or 1000. abs CACs = absolute coronary artery calcium score.

distributed and analyzing the data in 10-year strata might have led to more inaccurate calculations. Therefore, we deemed it appropriate to exclude those 3 studies, and accepted a loss of only 5% of the total data. We do not believe that eliminating 5% of the total data led to a significant bias. Obviously, the ultimate proof of the utility of our nomograms would come from the demonstration that they predict events more accurately than those currently available, and this important notion will need to be tested in prospective studies.

5. Conclusions

In this study our goal was to provide more generalizable age and sex based percentiles by pooling all available CAC score percentile studies across the world. We propose to use our CAC score percentile calculator as a new standard for percentile estimation, especially in underrepresented segments of the population such as women and the youth as well as Asian individuals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2020.01.006.

References

1. Goff Jr DC, et al. ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation.* 2013;129:S49–S73. https://doi.org/10.1161/01.cir.0000437741.48606.98 2014.
2. Piepoli MF, et al. European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR). *Eur Heart J.* 2016;37:2315–2381. https://doi.org/10.1093/eurheartj/ehw106 2016.
3. Peters SA, Bakker M, den Ruijter HM, Bots ML. Added value of CAC in risk stratification for cardiovascular events: a systematic review. *Eur J Clin Invest.* 2012;42:110–116. https://doi.org/10.1111/j.1365-2362.2011.02555.x.
4. Erbel R, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol.* 2010;56:1397–1406. https://doi.org/10.1016/j.jacc.2010.06.030.
5. Hecht HS. Coronary artery calcium scanning: the key to the primary prevention of coronary artery disease. *Endocrinol Metab Clin N Am.* 2014;43:893–911. https://doi.org/10.1016/j.ecl.2014.08.007.
6. Arnett DK, et al. ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation.* 2019. https://doi.org/10.1161/CIR.0000000000000678 CIR0000000000000678, 2019.
7. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. *J Am Coll Cardiol.* 2015;65:1552–1561. https://doi.org/10.1016/j.jacc.2015.02.020.
8. Budoff MJ, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2009;53:345–352. https://doi.org/10.1016/j.jacc.2008.07.072.
9. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113:30–37. https://doi.org/10.1161/circulationaha.105.580696.
10. Raggi P, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation.* 2000;101:850–855. https://doi.org/10.1161/01.cir.101.8.850.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151:264–269 W264.
12. Hopkins PN, et al. Association of coronary artery calcified plaque with clinical coronary heart disease in the National Heart, Lung, and Blood Institute's Family Heart Study. *Am J Cardiol.* 2006;97:1564–1569. https://doi.org/10.1016/j.amjcard.2005.12.043.
13. Park HE, et al. The prevalence and distribution of coronary artery calcium in asymptomatic Korean population. *Int J Cardiovasc Imag.* 2012;28:1227–1235. https://doi.org/10.1007/s10554-011-9922-2.
14. Budoff MJ, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol.* 2007;49:1860–1870. https://doi.org/10.1016/j.jacc.2006.10.079.
15. Gudmundsson EF, et al. Coronary artery calcium distributions in older persons in the AGES-Reykjavik study. *Eur J Epidemiol.* 2012;27:673–687. https://doi.org/10.1007/s10654-012-9730-6.
16. Hoff JA, et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol.* 2001;87:1335–1339. https://doi.org/10.1016/s0002-9149(01)01548-x.
17. Mitchell TL, et al. Age- and sex-based nomograms from coronary artery calcium scores as determined by electron beam computed tomography. *Am J Cardiol.* 2001;87:453–456. https://doi.org/10.1016/s0002-9149(00)01403-x a456.
18. Nasir K, et al. Coronary artery calcium volume scores on electron beam tomography in 12,936 asymptomatic adults. *Am J Cardiol.* 2004;93:1146–1149. https://doi.org/10.1016/j.amjcard.2004.01.043.
19. Pereira AC, et al. Age, gender, and race-based coronary artery calcium score percentiles in the Brazilian longitudinal study of adult health (ELSA-Brasil). *Clin Cardiol.* 2016;39:352–359. https://doi.org/10.1002/clc.22539.
20. Schmermund A, Erbel R, Silber S. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. *Am J Cardiol.* 2002;90:168–173. https://doi.org/10.1016/s0002-9149(02)02445-1.
21. Schmermund A, et al. Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. *Atherosclerosis.* 2006;185:177–182. https://doi.org/10.1016/j.atherosclerosis.2005.06.003.
22. Wong ND, Budoff MJ, Pio J, Detrano RC. Coronary calcium and cardiovascular event risk: evaluation by age- and sex-specific quartiles. *Am Heart J.* 2002;143:456–459. https://doi.org/10.1067/mhj.2002.120409.
23. Jang SY, Kim SM, Sung J, Cho SJ, Choe YH. Coronary artery calcium scores and cardiovascular risk factors in 31,545 asymptomatic Korean adults. *Int J Cardiovasc Imag.* 2016;32(Suppl 1):139–145. https://doi.org/10.1007/s10554-016-0892-2.
24. Ohmoto-Sekine Y, et al. Prevalence and distribution of coronary calcium in asymptomatic Japanese subjects in lung cancer screening computed tomography. *J Cardiol.* 2016;67:449–454. https://doi.org/10.1016/j.jjcc.2015.06.010.
25. Grundy SM, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation.* 2018;139:e1082–e1143. https://doi.org/10.1161/CIR.0000000000000625 2019.
26. Willemink MJ, et al. Coronary artery calcification scoring with state-of-the-art CT scanners from different vendors has substantial effect on risk classification. *Radiology.* 2014;273:695–702. https://doi.org/10.1148/radiol.14140066.
27. Willemink MJ, et al. Coronary calcium scores are systematically underestimated at a large chest size: a multivendor phantom study. *J Cardiovasc Comput Tomogr.* 2015;9:415–421. https://doi.org/10.1016/j.jcct.2015.03.010.
28. Becker CR, et al. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. *AJR Am J Roentgenol.* 2001;176:1295–1298. https://doi.org/10.2214/ajr.176.5.1761295.
29. Stanford W, Thompson BH, Burns TL, Heery SD, Burr MC. Coronary artery calcium quantification at multi-detector row helical CT versus electron-beam CT. *Radiology.* 2004;230:397–402. https://doi.org/10.1148/radiol.2302020901.
30. Budoff MJ, et al. Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the Multi-Ethnic Study of Atherosclerosis. *AJR Am J Roentgenol.* 2009;192:613–617. https://doi.org/10.2214/AJR.08.1242.
31. Reinsch N, et al. Comparison of dual-source and electron-beam CT for the assessment of coronary artery calcium scoring. *Br J Radiol.* 2012;85:e300–306. https://doi.org/10.1259/bjr/91904659.
32. Detrano RC, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility–MESA study. *Radiology.* 2005;236:477–484. https://doi.org/10.1148/radiol.2362040513.