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Coronary Artery Calcium Score and Polygenic Risk Score for the Prediction of Coronary Heart Disease Events

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IMPORTANCE Coronary artery calcium score and polygenic risk score have each separately been proposed as novel markers to identify risk of coronary heart disease (CHD), but no prior studies have directly compared these markers in the same cohorts.

OBJECTIVE To evaluate change in CHD risk prediction when a coronary artery calcium score, a polygenic risk score, or both are added to a traditional risk factor–based model.

DESIGN, SETTING, AND PARTICIPANTS Two observational population-based studies involving individuals aged 45 years through 79 years of European ancestry and free of clinical CHD at baseline: the Multi-Ethnic Study of Atherosclerosis (MESA) study involved 1991 participants at 6 US centers and the Rotterdam Study (RS) involved 1217 in Rotterdam, the Netherlands.

EXPOSURE Traditional risk factors were used to calculate CHD risk (eg, pooled cohort equations [PCEs]), computed tomography for the coronary artery calcium score, and genotyped samples for a validated polygenic risk score.

MAIN OUTCOMES AND MEASURES Model discrimination, calibration, and net reclassification improvement (at the recommended risk threshold of 7.5%) for prediction of incident CHD events were assessed.

RESULTS The median age was 61 years in MESA and 67 years in RS. Both log (coronary artery calcium+1) and polygenic risk score were significantly associated with 10-year risk of incident CHD (hazards ratio per SD, 2.60; 95% CI, 2.08-3.26 and 1.43; 95% CI, 1.20-1.71, respectively), in MESA. The C statistic for the coronary artery calcium score was 0.76 (95% CI, 0.71-0.79) and for the polygenic risk score, 0.69 (95% CI, 0.63-0.71). The change in the C statistic when each was added to the PCEs was 0.09 (95% CI, 0.06-0.13) for the coronary artery calcium score, 0.02 (95% CI, 0.00-0.04) for the polygenic risk score, and 0.10 (95% CI, 0.07-0.14) for both. Overall categorical net reclassification improvement was significant when the coronary artery calcium score (0.19; 95% CI, 0.06-0.28) but was not significant when the polygenic risk score (0.04; 95% CI, −0.05 to 0.10) was added to the PCEs. Calibration of the PCEs and models with coronary artery calcium and/or polygenic risk scores was adequate (all χ^2<20). Subgroup analysis stratified by the median age demonstrated similar findings. Similar findings were observed for 10-year risk in RS and in longer-term follow-up in MESA (median, 16.0 years).

CONCLUSIONS AND RELEVANCE In 2 cohorts of middle-aged to older adults from the US and the Netherlands, the coronary artery calcium score had better discrimination than the polygenic risk score for risk prediction of CHD. In addition, the coronary artery calcium score but not the polygenic risk score significantly improved risk discrimination and risk reclassification for CHD when added to traditional risk factors.

Supplemental content

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Risk assessment to match the intensity of preventive strategies with the absolute risk of an individual comprises the cornerstone of cardiovascular disease (CVD) prevention.[1,2] Guidelines recommend the use of multivariable risk models, such as the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations (PCEs),[3,4] European Society of Cardiology (ESC) SCORE2 model,[5,6] or the QRISK3 model[7,8] to estimate absolute risk of CVD. These models integrate data on demographics (age, sex) and established cardiovascular risk factors (blood pressure and cholesterol levels, diabetes status, and smoking status) to estimate risk.[5,9,10] Contemporary guidelines recommend a risk-based approach to aid in initiation of lipid-lowering therapy (eg, PCEs risk >7.5%) or intensive blood pressure lowering (eg, PCEs risk ≥10%) among middle-aged and older adults. However, conventional clinical risk scores provide an imprecise estimate of CHD risk.

Novel risk markers may improve risk estimation for CVD, particularly for coronary heart disease (CHD). Imaging of subclinical atherosclerosis with computed tomography (CT) to detect coronary artery calcium has been demonstrated to be a potent predictor of future clinical CHD.[11] Given that the estimated heritability of CHD ranges between 40% to 60%, polygenic risk scores have also been proposed as a tool to improve risk prediction and advance precision medicine. Polygenic risk scores quantify risk conferred by numerous common genetic variants and have been independently associated with risk of both subclinical atherosclerosis (coronary artery calcium)[12] and clinical CHD, suggesting that the polygenic risk score may be a more upstream risk marker.[13,14] Although coronary artery calcium previously has been compared with other risk markers, such as carotid intima-media thickness, high sensitivity C-reactive protein, and ankle-brachial index,[15] no prior studies have directly compared the change in risk discrimination and reclassification with the addition of a coronary artery calcium score, polygenic risk score, or both to traditional risk factor scores (eg, PCEs) when both scores are measured in the same cohort, which is necessary to allow for a head-to-head comparison. This was recently highlighted as a key knowledge gap in the 2022 AHA Scientific Statement on Polygenic Risk Scores for Cardiovascular Disease,[16] particularly with longer-term follow-up when the 2 risk scores may have greater predictive utility. To address this gap, data from 2 large community-based cohorts of middle-aged to older adults with up to 17 years of follow-up were analyzed to directly compare whether risk prediction would be more precise when a coronary artery calcium score or polygenic risk score is added to current prediction models.

Key Points

Question Does discrimination change when either a coronary artery calcium score or a polygenic risk score is added to a coronary heart disease (CHD) prediction model based on traditional risk factors?

Findings In 2 population-based studies involving 3208 adults aged 45 years through 79 years (Multi-Ethnic Study of Atherosclerosis [MESA], median age 61 years and the Rotterdam Study [RS], median age, 67 years) and of European ancestry, a coronary artery calcium score significantly improved discrimination when added to a traditional risk factor–based score (MESA, 0.09; Rotterdam Study, 0.06), but the polygenic risk score did not. Similar findings were observed when stratified by median age.

Meaning In middle-aged to older adults, the coronary artery calcium score but not the polygenic risk score improved CHD risk discrimination.

Methods

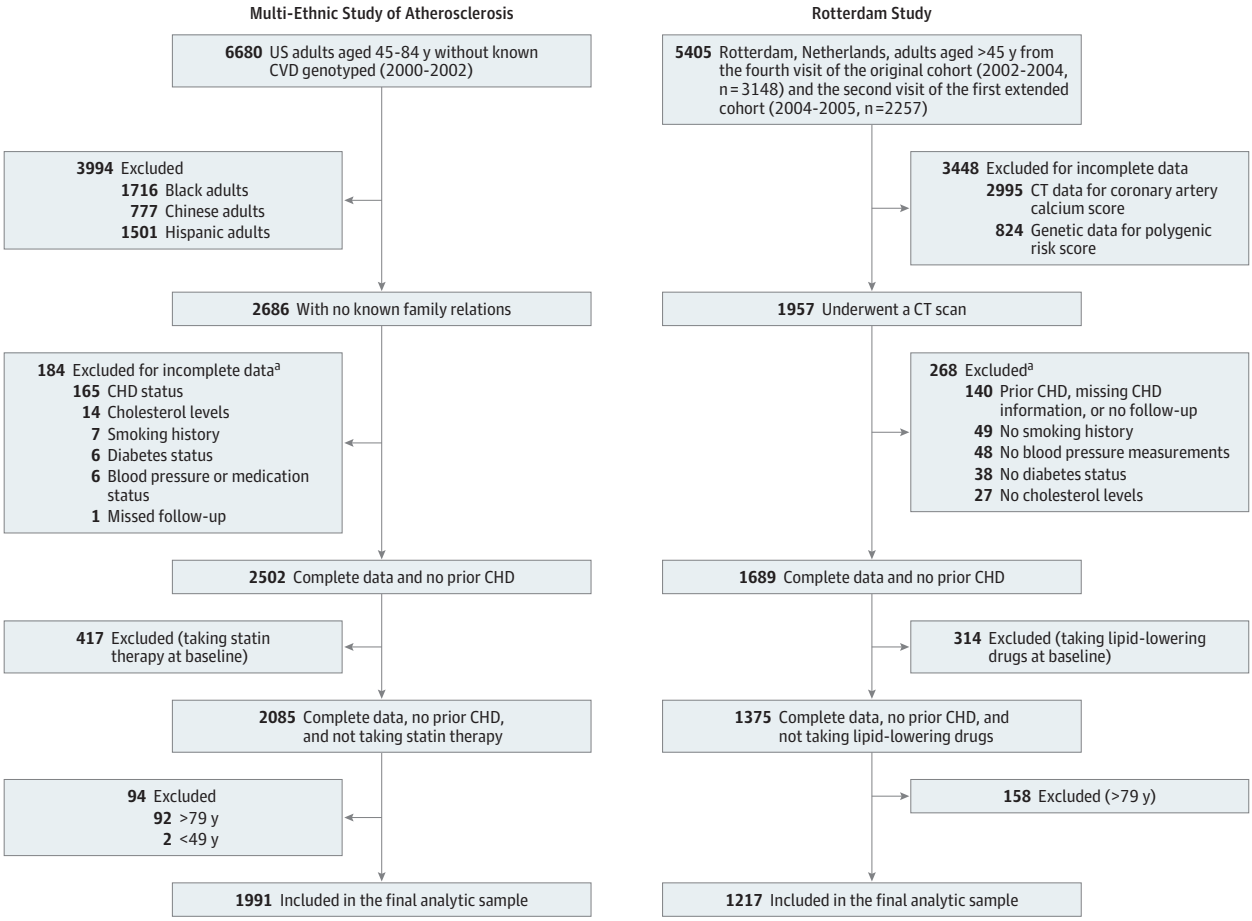
Study Population

We included data on participants aged 45 through 79 years without known CHD from 2 population-based cohort studies, the Multi-Ethnic Study of Atherosclerosis (MESA) and the Rotterdam Study(RS). Because the derivation and calibration of the polygenic risk score was completed in a largely European sample with well-established evidence of poorer performance among non-European samples, we included only individuals of European ancestry. In MESA, this was based on self-report of White race. In RS, this was based on genetic ancestry determined by principal components analysis.[17-19] Individuals with missing data or taking lipid-lowering therapy at baseline were excluded for a final analytic sample of 1991 in MESA and 1217 in RS (**Figure 1**). Individuals taking lipid-lowering therapy were excluded to help clarify when it would be clinically useful to initiate therapy according to current US recommendation guidelines.

The study design for MESA has been published.[20] Briefly, MESA recruited adults aged 45 to 84 years without known CVD from 6 centers across the US (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern New York City, New York; and St Paul, Minnesota) between July 2000 and September 2002. All MESA participants provided written informed consent, and the study was approved by institutional review boards at each study site. The study sample included participants with available data on risk factors, coronary artery calcium score, and genotyping at baseline.[21] Median follow-up was 16.0 (IQR, 12.7-16.7) years.

The RS is an ongoing, prospective, population-based cohort in the Netherlands of adults aged 45 years or older from the Ommoord district in the city of Rotterdam. Details on study design were described.[22,23] The first cohort started recruitment in 1990 (RS I) with 3 subsequent extensions (RS II, 2000; RS III, 2006; and RS IV, 2016). The RS has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). It has been entered into the Netherlands National Trial Register (NTR; http://www.trialregister.nl) and into the World Health Organization International Clinical Trials Registry Platform (ICTRP; https://www.who.int/clinical-trials-registry-platform) under shared catalog number NTR6831. All participants provided written informed consent. The median follow-up was 14.2 (IQR, 11.3-14.9) years.

Figure 1. Study Flow Diagram for the Analytic Samples From the Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study



[a] Participants may be excluded for more than 1 reason.

CHD indicates coronary heart disease; CT computed tomography; and CVD, cardiovascular disease.

CHD Risk Assessment Based on Traditional Risk Factors

All participants completed an in-person examination, which included (1) assessment of height, weight, and blood pressure; (2) self-report of behaviors and medications; and (3) phlebotomy for fasting blood sera samples for lipid levels. We applied the 2013 ACC/AHA PCEs to data from the baseline examination for MESA and the fourth visit of RS-I and second visit of RS-II to calculate the predicted 10-year risk of atherosclerotic CVD for each participant. The PCEs incorporate age, sex, smoking status (current vs none or former), systolic blood pressure, total and high-density lipoprotein cholesterol levels, type 2 diabetes status, and treatment for hypertension for adults aged 45 through 79 years.[3,10] In MESA, the published equation coefficients stratified by sex for White participants were applied. In RS, the PCEs were fitted to the RS sample to develop the PCEs-RS, which included the same predictors with cohort-specific coefficients to ensure adequate fit of the base model consistent with prior publications.

Novel Risk Markers

In MESA, the CT protocol and interpretation have been previously reported. Briefly, either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles County, and New York City) or a multidetector CT system (Baltimore, Forsyth County, and St Paul) were used. All participants were scanned twice over phantoms of known calcium concentration by certified technologists. The coronary artery calcium score was calculated at a central reading center by a radiologist or cardiologist using the Agatston method (Harbor-UCLA Research and Education Institute).[24] In RS, a 16-slice or 64-slice multidetector CT scanner (SOMATON, Siemens) was used, and coronary artery calcium was calculated using the Agatston method.

Genotype data for single-nucleotide polymorphisms (SNPs) were acquired on the Genome-Wide Human SNP Array 6.0 (Affymetrix) SNP array in MESA and the Illumina HumanHAP 550k BeadChip and Illumina Infinium HD Human660W-Quad BeadChip arrays in RS. SNPs were imputed using the standard 1000 Genomes cosmopolitan phase 3 version 5 reference haplotypes for both MESA and RS. We generated principal components using version 7.2.1 of the EIGENSOFT 7.2.1 package to adjust for population stratification. We calculated the CHD polygenic risk score for each participant based on the score developed by Khera et al[14] using the linkage disequilibrium SNP-reweighting approach that was composed of 6 630 149 million

SNPs. The SNP weights were based on the Coronary Artery Disease Genome Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics (CARDIOGRAMplusC4D) consortium and were downloaded from https://cvd.hugeamp.org/informational/data.

Outcome Ascertainment of CHD

All participants underwent interim in-person examination approximately every 18 months and participated in annual telephone follow-up conversations to ascertain any hospitalizations or acute events. In MESA, incident CHD was defined based on the following: myocardial infarction, definite or probable angina if followed by revascularization, resuscitated cardiac arrest, and CHD death. All CHD events were adjudicated by a study committee composed of physicians and epidemiologists with details previously published and protocol for the study available at http://www.mesa-nhlbi.org. In RS, incident CHD was defined as fatal or nonfatal myocardial infarction and CHD death with event adjudication by study physicians and a consulting cardiologist.[25]

Statistical Analysis

Summary statistics of baseline demographics in MESA and RS were defined using mean (SD), percentages of participants, and median (IQR). All analyses were performed separately in each cohort. Hazard ratios (HRs) were estimated with Cox proportional hazards models to examine the association between an SD change in each predictor (PCEs or PCEs-RS [%], coronary artery calcium score [transformed as log coronary artery calcium+1], and polygenic risk score [standardized to *z* score]) and incident CHD. The proportionality assumption was tested by Schoenfeld residuals, which was met for both studies. All analyses were adjusted for age, sex, study site for MESA or cohort RS, and the top 5 principal components of ancestry. Model performance, including discrimination (Harrell C statistic), calibration (comparing observed vs expected event probabilities visually and with the Greenwood-Nam-D'Agostino χ^2 test), and change in risk stratification (continuous and categorical net reclassification improvement [NRI], integrated discrimination improvement [IDI]), was assessed. The primary outcome was the change in model discrimination or ΔC statistic when either coronary artery calcium, polygenic risk score, or both were added to the PCEs. The C statistic was used as the primary metric of risk discrimination based on published recommendations by an AHA scientific statement[26] and an expert consensus panel for improving reporting standards for polygenic risk score.[27] Subgroup analysis was conducted stratified by median age. Sensitivity analysis was performed in MESA excluding angina events from the CHD outcome. Additionally, cumulative incidence of CHD was calculated in both MESA and RS stratified by coronary artery calcium score (0, 1-100, 101-300, and >300 AU, higher scores indicate worse outcomes) and polygenic risk score categories (<50%, 50%-80%, and >80%, higher percentiles indicate worse risk). CIs for the C statistics and ΔC statistic were estimated using bootstrapping 1000 times. A 2-sided *P* value < .05 was considered statistically significant. Statistical analyses were performed in R software, version 4.1.0 (MESA) and version 4.03 (RS).

Results

Study Sample

Among the 1991 participants from MESA and 1217 participants from RS, the mean age was 61 (SD, 10) years and 68 (SD, 5) years, respectively, with little more than half of each sample being female (**Table 1**). The median predicted atherosclerotic CVD risk based on traditional risk factors was 6.99% in MESA and 5.93% in RS. During the total available follow-up in MESA (median, 16.0 years) and RS (median, 14.2 years), incident CHD occurred in 187 (9.4%) and 98 (8.1%), respectively, with the breakdown of each CHD subtype in eTable 1 in Supplement 1.

Coronary Artery Calcium and Polygenic Risk Score With Incident CHD

Coronary artery calcium and polygenic risk scores were significantly associated with CHD with a similar magnitude of association in both studies (eTable 2 in Supplement 1). Cumulative incidence estimates stratified by coronary artery calcium score (0, 1-100, 101-300, and >300) and polygenic risk score categories (<50%, 50%-80%, and >80%) are displayed in **Figure 2**; eFigure 1, and eTables 3 and 4 in Supplement 1. Higher rates of CHD were observed in categories with higher coronary artery calcium scores with a dose-response relationship in both studies. In contrast, rates of CHD were similar with overlapping 95% CIs between a polygenic risk score of less than 50% and between 50% and 80%, but was higher for those with scores higher than 80%.

Model Performance

For CHD events, the area under the curve for each novel marker in MESA and RS is displayed in **Figure 3** and eFigure 2 in Supplement 1. In MESA, the C statistic associated with the coronary artery calcium score was 0.76 (95% CI, 0.71 to 0.79) and for the polygenic risk score was 0.69 (95% CI, 0.63 to 0.71; **Table 2**; eTable 5 in Supplement 1). The change in C statistic when coronary artery calcium was added to PCEs was 0.09 (95% CI, 0.06 to 0.13), and there was no significant change in the C statistic when the polygenic risk score was added to the PCEs. Continuous NRI and IDI were significant for the addition of either scores. Overall categorical NRI was only significant when the coronary artery calcium score (0.19; 95% CI, 0.06 to 0.28) but not the polygenic risk score (0.04; 95% CI, −0.05 to 0.10) were added to the PCEs (eTables 6 and 7 in Supplement 1). The event, nonevents, and percent reclassified for MESA are displayed in eTable 8 in Supplement 1. Similar patterns and estimates for the C statistic, change in C statistic, NRI, and IDI were observed in RS (Table 2; eTables 6-8 in Supplement 1).

Model calibration was adequate when assessed visually (eFigures 3-5 in Supplement 1) and quantitatively (eTable 9 in Supplement 1) with χ^2 less than 20 for all the models examined, including the modified RS PCEs risk model. Subgroup analysis stratified at the median age in both studies demonstrated similar results (eTables 10 and 11 in Supplement 1). Sensitivity analysis excluding angina from the CHD end point in MESA demonstrated consistent results (eTable 12 in Supplement 1).

Table 1. Baseline Characteristics, Risk Scores, and Incident Coronary Heart Disease Rates: Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study

	MESA (n = 1991)	Rotterdam Study (n = 1217)
Descriptive characteristics		
Age, mean (SD), y	61.2 (9.7)	67.6 (4.8)
Female, No. (%)	1059 (53)	629 (52)
Male, No. (%)	932 (47)	588 (48)
At least high school education, No. (%)	1904 (96)	618 (51)
Current smoking, No. (%)	249 (12.5)	149 (12.2)
Former smoking, No. (%)	862 (43.3)	706 (58.0)
Never smoking, No. (%)	880 (44.2)	363 (29.8)
BMI, mean (SD)	27.6 (5.2)	27.6 (3.8)
SBP, mean (SD), mm Hg	122 (20)	145 (20)
Hypertension, No. (%)	671 (33.7)	813 (66.8)
Antihypertensive medication, No. (%)	557 (28)	341 (28)
Type 2 diabetes, No. (%)	100 (5)	131 (11)
Total cholesterol, mean (SD), mg/dL	200 (35)	228 (35)
HDL cholesterol, mean (SD), mg/dL	53 (16)	56 (15)
Hyperlipidemia, No. (%)[a]	233 (12)	410 (34)
CHD risk markers		
Atherosclerotic CVD risk based on traditional risk factor, median (IQR), %[b]	6.99 (2.69-15.80)	5.93 (2.87-10.68)
CAC score, median (IQR), AU[c]	1.4 (0-108.8)	34.6 (0.9-198.1)
PRS, median (IQR)[d]	18.06 (18.00-18.12)	17.14 (16.99-17.21)
CHD follow-up		
Total follow-up, median (IQR), y	16.0 (12.7-16.7)	14.2 (11.3-14.9)
Total incident CHD events, No. (%)[e]	187 (9.4)	118 (9.7)

Abbreviations: AU, Agatston units; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; coronary heart disease; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; PRS, polygenic risk score; RS, Rotterdam Study; SBP, systolic blood pressure.

SI conversion factor: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

[a] Defined as total cholesterol greater than or equal to 240 mg/dL or taking medication.

[b] Risk is based on a multivariable risk prediction model of a 10-year atherosclerotic CVD risk based on fixed (sex, age, and race) and predefined modifiable risk factors. The 2013 ACC/AHA Pooled Cohort Equations (PCEs) were used in MESA to estimate risk based on traditional risk factors and a modified version of PCEs (PCE-RS) was used in RS with cohort-specific coefficients. Predicted atherosclerotic CVD risk of 7.5% or greater is considered higher risk, whereby an individual may benefit from lipid-lowering therapy.

[c] CAC is a directly quantified continuous measure of coronary calcium burden derived from computed tomographic imaging. CAC is scored as 0 or greater with higher numbers indicating greater calcium burden and therefore higher risk of coronary artery disease.

[d] PRS is a continuous value representing the weighted burden of disease-associated common genetic variants for an individual. A higher PRS is indicative of higher risk of coronary artery disease (there is no set score that leads to intervention).

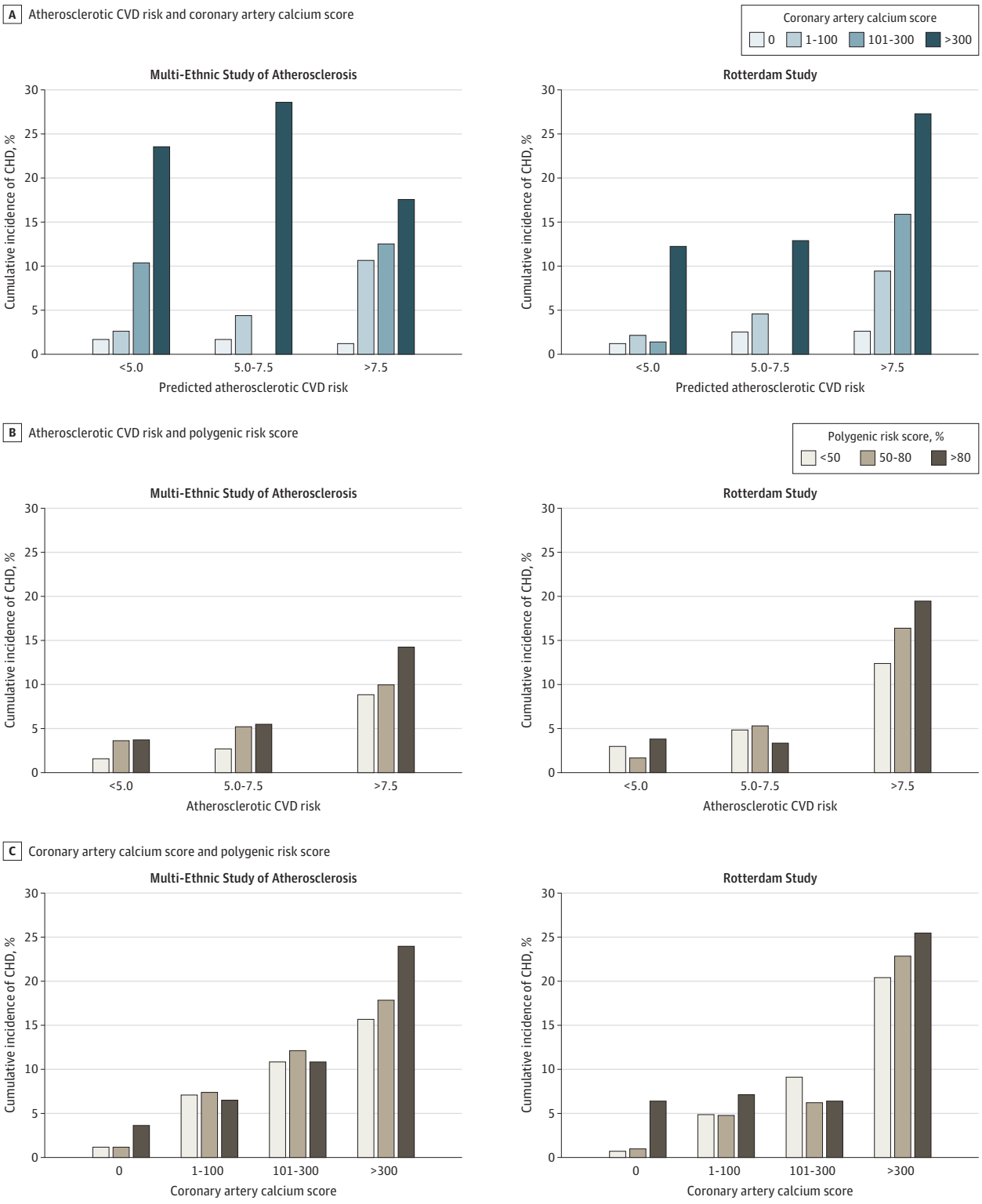
[e] In MESA, incident CHD was defined as myocardial infarction, definite or probable angina if followed by revascularization, resuscitated cardiac arrest, and CHD death. In RS, incident CHD was defined as fatal or nonfatal myocardial infarction and CHD death.

Discussion

To our knowledge, this is the first study to perform a head-to-head comparison of the coronary artery calcium and polygenic risk scores for predicting risk of CHD in 2 large, well-established cohorts of middle-aged and older adults with up to 17 years of follow-up. When the coronary artery calcium score was added to a traditional risk factor–based model, there was a statistically significant and clinically meaningful improvement in risk discrimination (increase in the C statistic) and risk stratification (NRI). In contrast, when the polygenic risk score was added to a traditional risk factor–based model, the change in risk discrimination and categorical net reclassification improvement was not statistically significant. The combination of the 2 scores had no additive predictive utility (discrimination or risk stratification) compared with when the coronary artery calcium score was added to a traditional risk factor–based model. These findings were consistent in both younger and older participants when stratified by the median age in MESA (45-61 years and 62-79 years) and RS (45-68 years and 69-79 years).

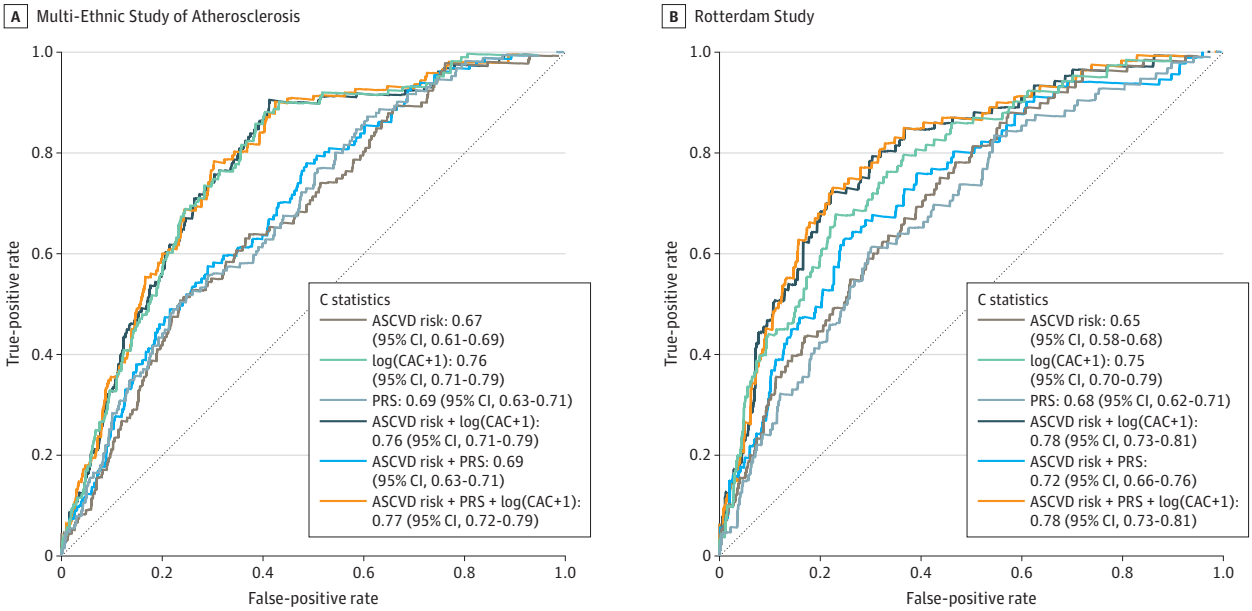
This study directly addresses a key knowledge gap identified by the recent AHA Scientific Statement, among others, expressing a need to directly compare polygenic risk scores with coronary artery calcium scores for predicting risk of CHD.[16] The present study is the first, to our knowledge, to compare risk discrimination with polygenic risk score and coronary artery calcium score in the same analytic sample as is needed to inform a direct comparison of these 2 novel markers. Given that prior studies have demonstrated a significant association between the polygenic risk score and the

Figure 2. Incident Coronary Heart Disease Stratified by Traditional Risk Factor Score, Coronary Artery Calcium Score, and Polygenic Risk Score: Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study



For a definition of atherosclerotic CVD risk, coronary artery calcium score, polygenic risk score as applied to MESA and the Rotterdam Study, see the footnotes in Table 1.

Figure 3. Receiver Operator Characteristic Curves and C Statistics for Prediction of Coronary Heart Disease in the Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study



For a definition of atherosclerotic cardiovascular disease (ASCVD) risk, coronary artery calcium (CAC) score, polygenic risk score (PRS) as applied to the Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study, see the footnotes in Table 1.

Table 2. Model Discrimination for Prediction of Incident Coronary Heart Disease: Multi-Ethnic Study of Atherosclerosis and the Rotterdam Study[a]

	C statistic (95% CI)						Change in C statistic (95% CI)		
Study cohort[b]	Model 1: atherosclerotic CVD risk based on risk factor	Model 2: log (CAC+1)	Model 3: PRS	Model 4: atherosclerotic CVD risk + log (CAC+1)	Model 5: atherosclerotic CVD risk + PRS	Model 6: atherosclerotic CVD risk + PRS + log (CAC+1)	Model 4 vs model 1	Model 5 vs model 1	Model 6 vs model 1
MESA	0.67 (0.61 to 0.69)	0.76 (0.71 to 0.79)	0.69 (0.63 to 0.71)	0.76 (0.71 to 0.79)	0.69 (0.63 to 0.71)	0.77 (0.72 to 0.79)	0.09 (0.06 to 0.13)	0.02 (0 to 0.04)	0.10 (0.07 to 0.14)
Rotterdam study	0.65 (0.58 to 0.68)	0.75 (0.70 to 0.79)	0.68 (0.62 to 0.71)	0.78 (0.73 to 0.81)	0.72 (0.66 to 0.76)	0.78 (0.73 to 0.81)	0.07 (0.04 to 0.12)	0.02 (0 to 0.04)	0.08 (0.04 to 0.12)

Abbreviations: CVD, cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; PRS, polygenic risk score.

[a] See Table 1 footnotes for the definitions of atherosclerotic CVD, CAC, and PRS and for the definitions of CHD for each study.

[b] All models include age, sex, top 5 principal components of ancestry, study site (in MESA), and cohort (in RS).

coronary artery calcium score[12,28] and have demonstrated that the polygenic risk score significantly improves risk prediction of coronary artery calcium compared with risk factors alone,[29] it is possible that the polygenic risk score and coronary artery calcium score may each be clinically relevant at different life stages. The polygenic risk score estimates inherited risk or susceptibility based on common genetic variants whereas the coronary artery calcium score represents subclinical disease burden. Although the current findings demonstrate similar results when stratifying by median age, the median age in these samples was in the 60s. In contrast, prior studies from the UK biobank have suggested the potential utility of the polygenic risk score for adults aged 40 years through 49 years where pooled PCEs have poorer model performance (age, 40-49 years).[30-32] Beyond risk prediction, whether communication of risk with improved risk quantification will translate into improved outcomes requires further study to influence clinical practice. This is currently being investigated in the context of a clinical trial to determine differences in cholesterol levels and adherence to statin therapy based on risk estimated by PCEs and coronary artery calcium scores or PCEs and polygenic risk score among a middle-aged to older population in Victoria, Australia.[33]

Although coronary artery calcium scores demonstrated excellent risk discrimination and reclassification in this study, adding the polygenic risk score to it did not meaningfully improve these measures of risk prediction. Although the continuous NRI and IDI were significant for both scores, the categorical NRI, which is clinically relevant based on treatment thresholds, was only significant for coronary artery calcium. Furthermore, among individuals with a coronary artery calcium score of 0, which is one of the strongest negative risk markers for future cardiovascular events and mortality,[34,35] the polygenic risk score did not further risk

stratify individuals in this low-risk group with overlapping estimates of cumulative incidence of CHD in the high- (>80%) vs low-polygenic-risk score (<50%) groups. Similar findings were recently reported separately from the MESA cohort,[36] but it is newly demonstrated in RS. A recent analysis from the Coronary Artery Risk Development in Young Adults study demonstrated a greater risk of CHD in the highest vs lowest quintile of polygenic risk score among the subset of White individuals with coronary artery calcium of 0 (HR, 4.1; 95% CI, 1.1-15.1). Although this suggests that the polygenic risk score may be useful for younger adults who have yet to develop coronary artery calcium, this study did not evaluate risk prediction metrics for this group.[37] In MESA and RS, cumulative incidence of CHD was high in all polygenic risk score groups (>7.5%) among those with extensive coronary artery calcium (>300). This suggests that a low polygenic risk score would not be clinically useful to revise an individual's risk estimate. In contrast, the polygenic risk score has been proposed to guide intensification of newer lipid-lowering therapies (eg, proprotein convertase subtilisin/kexin type 9 inhibitors) in high-risk subsets and requires further study.[38]

The current study findings are consistent with the ACC/AHA,[10] ESC,[9] and American Society for Preventive Cardiology[39] guidelines that prioritize the inclusion of the coronary artery calcium score over the polygenic risk score for predicting risk of CHD. The latest ACC/AHA[10] Guidelines for Primary Prevention from 2019 did not mention use of the polygenic risk score and instead recommended coronary artery calcium to refine risk estimation for selected individuals with borderline to intermediate risk. The ESC guidelines[9] briefly mentioned polygenic risk score but stated that adequate data were not available to inform its use in the primary prevention of CHD. However, no direct comparison between coronary artery calcium and polygenic risk score was available until the current study, which demonstrated that discrimination and reclassification were improved with a coronary artery calcium score but did not demonstrate that the same improvement existed with the polygenic risk score in a general population of middle-aged to older adults. These data support the caution for integration of genetic information when there is limited clinical utility as recently highlighted by the American College of Physicians.[40]

Limitations

This study has several limitations. First, the risk estimated by traditional risk factors was operationalized with the PCEs in MESA, which was derived and validated in a US sample for atherosclerotic CVD events that included CHD and stroke. The inclusion of CHD as the end point of interest was based on the primary objective of this analysis assessing markers of CHD risk: polygenic risk score and coronary artery calcium. That may mean that the change in discrimination with either risk marker is actually lower than estimated in this analysis. In addition, modifying the PCEs to apply to the European cohort in RS may bias the findings. However, this was necessary to address the focused analytic question of the additive utility of the coronary artery calcium score, the polygenic risk score, or both when compared with traditional models that are based on risk factors. Therefore, it was necessary to ensure appropriate fit of the base model so that the additive utility of either marker was not artificially inflated. This approach was based on published recommendations and was consistent with that used in prior analyses when PCEs were applied to European samples.[30,41] The results were highly consistent across the US (MESA) and European (RS) samples and suggest generalizability to both a US and European context.

Second, the sample only included White individuals or individuals of European ancestry because derivation of the polygenic risk score in this population and because of its poor discrimination in adults who do not have European ancestry.[42] Therefore, addressing the study question for a diverse sample of adults was not possible, thereby prohibiting assessing generalizability of the present findings and enhancing equity in genomics research. It is possible that a transethnic polygenic risk score may have better discrimination among minoritized populations for whom the PCEs have been documented to underperform.[43,44] Ongoing efforts to expand risk prediction studies that examine multiancestry CHD polygenic risk scores in diverse populations are needed.[45]

Third, the analysis focused on middle-aged to older adults. The direct comparison of predictive utility of a polygenic risk score and coronary artery calcium score among younger adults has not been studied and broad gaps remain in evidence-based recommendations to estimate and manage atherosclerotic CVD risk among younger adults.[46] Two recent analyses demonstrated significant but small changes in discrimination when a polygenic risk score was added to traditional risk factors in cohort studies of young adults aged 20 through 39 years.[37,47]

Fourth, the baseline examination for the analytic samples are from the early 2000s, which may limit its generalizability for contemporary clinical practice. However, the most up-to-date adjudicated outcomes were used and captured with up to 17 years of follow-up. In addition, the selection of these 2 cohorts was predicated on the need for available data on traditional risk factors, coronary artery calcium score, and polygenic risk score in the same analytic sample.

Fifth, there were differences in the definition of CHD and duration of follow-up across the 2 cohorts. However, a sensitivity analysis in MESA for hard CHD, excluding angina, revealed consistent findings. Although the PCEs were derived and validated for 10 years of follow-up, longer-term follow-up in MESA with a median of 16 years demonstrated similar magnitude of association between risk markers and CHD and CHD risk discrimination.

Sixth, the present analysis did not develop new predictive equations with the novel markers given that the focus on the question: What is the incremental predictive utility when these markers are added to contemporary standard-of-care risk-prediction equations. Future studies developing and validating new optimally predictive equations that incorporate the coronary artery calcium and/or the polygenic risk score with conventional and innovative statistical approaches (eg, machine learning) should be considered.

Conclusions

In this binational analysis of White adults from 2 community-based cohorts, both coronary artery calcium and polygenic risk scores were significantly associated with incident CHD. However, the addition of coronary artery calcium, but not polygenic risk score, to the PCEs improved risk discrimination with consistent estimates in both cohorts studied and with up to 17 years of follow-up.

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Additional Information: The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; http://www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; https://www.who.int/clinical-trials-registry-platform) under shared catalog number NTR6831.

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