Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort

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Aims	To evaluate the 2013 American Heart Association (AHA)-American College of Cardiology (ACC)-Atherosclerotic Cardiovascular Disease (ASCVD) risk score among four different race/ethnic groups and to ascertain which factors are most associated with risk overestimation by the AHA-ACC-ASCVD score.
Methods and results	The Multi-Ethnic Study of Atherosclerosis (MESA), a prospective community-based cohort, was used to examine calibration and discrimination of the AHA-ACC-ASCVD risk score in 6441 White, Black, Chinese, and Hispanic Americans (aged 45–79 years and free of known ASCVD at baseline). Using univariable and multivariable absolute risk regression, we modelled the impact of individual risk factors on the discordance between observed and predicted 10-year ASCVD risk. Overestimation was observed in all race/ethnic groups in MESA and was highest among Chinese (252% for women and 314% for men) and lowest in White women (72%) and Hispanic men (67%). Higher age, Chinese race/ethnicity (when compared with White), systolic blood pressure (treated and untreated), diabetes, alcohol use, exercise, lipid-lowering medication, and aspirin use were all associated with more risk overestimation, whereas family history was associated with less risk overestimation in a multivariable model (all $P < 0.05$).
Conclusion	The AHA-ACC-ASCVD risk score overestimates ASCVD risk among men, women, and all four race/ethnic groups evaluated in a modern American primary prevention cohort. Clinicians treating patients similar to those in MESA, particularly older individuals and those with factors associated with more risk overestimation, may consider interpreting absolute ASCVD risk estimates with caution.
Keywords	Cardiovascular risk prediction • Prevention • Risk factors

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Introduction

In November 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) published a new atherosclerotic cardiovascular disease (ASCVD) risk score to guide ASCVD risk-reducing therapy.[1] This new risk score was derived from four prospective cohort studies that enrolled participants between the years of 1965 and 1995.[1-5] The applicability of these new pooled cohort equations, also known as the AHA-ACC-ASCVD risk score, to modern populations has been questioned, as it has been found to overestimate risk in several independent cohorts.[1,6-8] Overestimation was attenuated in one study when the cohort was restricted to subjects that met criteria consistent with guideline recommendations for the use of the AHA-ACC-ASCVD risk score to guide statin therapy [not taking lipid-lowering medication at baseline and having low-density lipoprotein cholesterol (LDL-C) between 70 and 189 mg/dL].[8] We have previously reported that the 2013 AHA-ACC-ASCVD and three older Framingham-based risk scores overestimated cardiovascular events by 37–154% in men and 8–67% in women in the more modern Multi-Ethnic Study of Atherosclerosis (MESA) cohort, with overestimation noted throughout the continuum of risk.[9] However, questions have been raised about the relevance of MESA, as it is multi-ethnic and may represent a healthier subset of the general US population.

We first sought to compare MESA to The National Health and Nutrition Examination Survey (NHANES) data to better understand the applicability of these results to the greater US population. While the AHA-ACC-ASCVD risk score is recommended only for individuals who identify themselves as White or Black, we sought to examine the performance of the new risk score in four different race/ethnicities and to determine if the risk factors included in the AHA-ACC-ASCVD risk score impact ASCVD risk differently in White and Black individuals. Finally, we undertook additional analyses to quantify the impact of differences in age, gender, race/ethnicity, blood pressure, serum cholesterol, family history of heart attack, socio-economic status, lifestyle variables, and preventive therapies (aspirin, lipid-lowering, anti-hypertensive, and interim revascularization) common to modern cohorts, on risk score overestimation. We reasoned that such data may be useful in the implementation of ASCVD prevention strategies as well as future risk score and guideline development.

Methods

The Multi-Ethnic Study of Atherosclerosis is a prospective community-based epidemiologic study of cardiovascular disease in an age- and gender-balanced, multi-ethnic cohort free of known ASCVD at the time of enrolment. The study design and methods have been previously published.[10] The Multi-Ethnic Study of Atherosclerosis has institutional review board approval at all six enrolment sites. Atherosclerotic cardiovascular disease events during study follow-up consisted of myocardial infarction (MI), definite or probable angina, resuscitated cardiac arrest, coronary heart disease (CHD) death, stroke (not transient ischaemic attack), stroke death, other atherosclerotic death, or other CVD death. A detailed description of the MESA methodology is available at www.mesa-nhlbi.org. Race/ethnicity was self-reported. Family history of CHD was considered positive at the baseline visit if either parent had suffered a

heart attack. The AHA-ACC-ASCVD risk prediction score was calculated from the baseline MESA data (2000–02) using published equations, using the equations for White individuals to calculate risk in Chinese and Hispanics.[1] The Multi-Ethnic Study of Atherosclerosis included participants between the ages of 45 and 84 years; the AHA-ACC-ASCVD risk calculator is recommended for individuals aged 40–79 years. Therefore, in this study, our cohort was limited to individuals aged 45–79. Additional exclusion of participants with missing data required for risk score calculation ($n = 53$, $<1\%$), or no follow-up data after baseline ($n = 3$, $<1\%$), resulted in a final sample size of 6441.

To assess comparability to nationally representative samples, demographic and ASCVD risk factors were detailed for the AHA-ACC-ASCVD risk score derivation cohort, MESA participants included in this study, and the ASCVD-free, non-pregnant US population ages 40–79 as reflected in NHANES data 2013–14.[11] Cumulative measure of ASCVD risk factor prevalence was assessed by calculating the percentage of participants with a calculated AHA-ACC-ASCVD risk score of <5, 5–7.4, 7.5–9.9, and $\geq 10\%$ 10-year risk in the MESA cohort and the ASCVD-free, non-pregnant US population ages 40–79 in NHANES survey (2007–10).[1] Rates of anti-hypertensive and lipid-lowering medication use in MESA were also compared with the US adult population estimates.[12,13] For these analyses, MESA data are weighted by direct age-adjustment method to the year 2000 projected US population.[13]

Observed and expected events for the AHA-ACC-ASCVD score, stratified by race/ethnicity and gender, were compared in MESA. Events were censored at 10 years of follow-up. For the 6072 participants who did not have an ASCVD event, 62% had ≥ 10 years of follow-up and 88% had >9 years of follow-up data. For each subject with <10 years of follow-up, including those who died, we lowered their 10-year risk estimate to correspond to their length of follow-up using an exponential survival function to scale the risk score. If A10 denotes the 10-year proportion with events according to the AHA-ACC-ASCVD risk score, then the 1-year proportion is $A1 = -\ln(1-A10)/10$. So for a person with 8.5 years of follow-up, $A8.5 = 1 - \exp(-A1 \times 8.5)$.

To evaluate if ASCVD risk factors included in the AHA-ACC-ASCVD risk model impact Black individuals differently from Whites, adjusted and unadjusted Cox models for ASCVD were used to calculate hazard ratios for Black men and women compared with White men and women, and modelling the interaction between race and each of the risk factors in the ASCVD-ACC-ASCVD risk score was performed. Estimation of the AHA-ACC-ASCVD Cox model in MESA was performed to compare the magnitude of individual risk factors coefficients used in the AHA-ACC-ASCVD risk score to those obtained fitting the same model in the MESA cohort. For comparison, the same analysis was performed for the Reynolds risk score[14,15] and The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III[16] risk score in MESA.

Univariable and multivariable absolute risk regression was used to evaluate the impact of individual risk factors on the discordance between observed ASCVD and predicted ASCVD by the AHA-ACC-ASCVD risk score. The absolute risk model is a linear regression model at the individual level, predicting a dichotomous outcome (ASCVD event yes/no within 10 years). It was fit as a generalized linear model with the AHA-ACC-ASCVD risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors.[17-19] To this model, we add other covariates either individually or jointly. Since almost every subset exhibited overestimation, we present the negative of the coefficients from the model—this allows us to talk about differences in 'more' overestimation (as opposed to negative 'less' overestimation). As an example, consider the model that adds gender alone. By fixing the coefficient of the AHA-ACC-ASCVD risk score to 1.0, the interpretation of the gender coefficient

is the average difference in overestimation in predicted risk for men when compared with women. Both men and women are overestimated, but men are significantly more so. The multivariable model allows us to explore, for instance, whether this difference is due to men and women having different distributions of other risk factors and thus evaluate the independent contribution of various subgroups.

Our model was carefully selected to (i) include the variables that were part of the risk equation, (ii) include baseline covariates that were hypothesized to be responsible for the AHA-ACC-ASCVD risk score's poor fit in MESA, such as higher socio-economic status, and (iii) to account for time-updated medical treatments that were believed to reduce the risk of ASCVD, and therefore cause 'overestimation' by the risk calculator. Fit statistics were not used to modify the models, nor was statistical significance of any particular parameter. This approach allowed us to evaluate the impact of age, gender, race/ethnicity, socio-economic status, lifestyle variables, family history of acute MI, blood pressure, serum cholesterol, and individual preventive therapies (aspirin, lipid-lowering, anti-hypertensive) on the discordance between AHA-ACC-ASCVD calculated risk and the observed events. Individual preventive therapies were measured at baseline and during four follow-up visits; ASCVD event surveillance included assessment at all follow-up visits and 12 additional scheduled phone interviews. Therapies and events were treated as time-updated in the model. In an effort to study revascularizations that may have prevented subsequent events, all revascularizations >5 days prior to an event, or revascularizations not followed by any event, were selected for modelling.

Sensitivity analyses were performed on MESA participants who met clinical criteria consistent with guideline recommendations for the use of the AHA-ACC-ASCVD risk score to guide statin therapy (not taking lipid-lowering medication at baseline and having an LDL-C level between 70 and 189 mg/dL).[1] Additional sensitivity analyses were performed by including potential ASCVD events identified in the Part A hospital claims Centers for Medicare & Medicaid Services (CMS) billing database, at any point during follow-up, but not adjudicated as an ASCVD event by MESA.

Results

With the exception of age, ethnic diversity, and HDL cholesterol, MESA participants included in this analysis appear to be more representative of contemporary Americans, as reflected in 2013–14 NHANES data, than subjects included in the AHA-ACC-ASCVD derivation cohort (*Table 1*). In addition to individual risk factors, aggregate cardiovascular risk profiles in MESA appeared similar to contemporary Americans in NHANES as evident from a comparable proportion (within 3%) of subjects with a calculated AHA-ACC-ASCVD risk score of <5, 5–7.4, 7.5–9.9, and ≥10% (Supplementary material online, *Table S1*). Baseline and treatment trends were also similar in MESA and NHANES. At baseline (2000–02), 31% of MESA participants (age-adjusted) were treated for hypertension when compared with ∼30% of the US population in contemporary NHANES data (2001–02).[12] Cholesterol-lowering medication use was reported in 20% of the US population older than 40 years in NHANES 2003–04 and in 19% of age-adjusted MESA participants at approximately the same time (2002–04). These percentages

Table 1 Baseline characteristics of Multi-Ethnic Study of Atherosclerosis subjects used in this analysis, American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease derivation cohort, and non-pregnant Americans free of known atherosclerotic cardiovascular disease between ages 40 and 79 per National Health and Nutrition Examination Survey 2013–14

Variables, mean (SD)	MESA	AHA-ACC-ASCVD derivation cohort	NHANES 2013–14[a]
Age (years)	61.3	56.3	55.6
Age range	45–79	40–79	40–79
Gender (% female)	52.6	56.4	52.6
Ethnicity, *n* (%)			
White	38.5	82.6	69.3
Chinese	11.9	0	[b]
Black	27.6	17.4	11.0
Hispanic	22.1	0	12.3
Total cholesterol (mg/dL)	194.4	215.5	196.4
HDL cholesterol (mg/dL)	50.9	52.6	54.3
Untreated SBP (mmHg)	121.2	123.1	121.3
Treated SBP (mmHg)	134.3	136.1	131.3
Current smoker (%)	13.5	25.6	18.7
Diabetes[c] (%)	11.5	9.1	12.8
Baseline anti-hypertensive medication use (%)	36.4	21.2	36.6

[a]NHANES data includes non-pregnant participants ages 40–79 without prior self-reported MI or stroke. Data are weighted using the full sample 2-year mobile exam centre weight.
[b]NHANES collected information about Asian ethnicity, whereas MESA collected data from Chinese participants specifically.
[c]For MESA, diabetes was defined as use of insulin/oral hypoglycaemic agents or fasting glucose ≥126 mg/dL. For NHANES, diabetes status was ascertained by participant's report of diabetes diagnosis from a doctor.

increased to an estimated 28% of US adults in 2011–12 and 34% of participants in MESA over the same time period.[13]

In MESA, risk overestimation was similar for women (100%) and men (93%) as was discrimination: c-statistic = 0.74 for women and 0.71 for men (Table 2). That is, observed rates were roughly half of that predicted by the risk score. Overestimation was observed in all race/ethnicity groups in the MESA cohort and was highest among Chinese (252% for women and 314% for men), and lowest in White women (72%) and Hispanic men (67%). A sensitivity analysis limited to MESA participants that met criteria consistent with guideline recommendations for the use of the AHA-ACC-ASCVD risk score to guide statin therapy (not taking lipid-lowering medication at baseline with an LDL-C between 70 and 189 mg/dL) produced similar

overestimation as seen in the primary analysis with the exception that the lowest discordance between observed and calculated ASCVD event rates was seen in Hispanic men (71%) and women (49%) (Table 3). Sensitivity analyses to account for the possibility of missed events by including 20 un-adjudicated MI events identified in the CMS database were consistent with overall study results (Table 4 and Supplementary material online, Table S2). In Cox models that included all ASCVD risk factors present in the AHA-ACC-ASCVD risk score, the hazard ratios for ASCVD events in Black men compared with White men and the hazard ratios for Black women compared with White women were not significant in MESA ($P = 0.285$ and 0.350, Supplementary material online, Table S3). The lack of statistical significance indicates that race differences with

Table 2 Atherosclerotic cardiovascular disease events predicted via the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score and atherosclerotic cardiovascular disease events observed among Multi-Ethnic Study of Atherosclerosis participants aged 45–79, stratified by gender and race/ethnicity

Risk score	n	Predicted events, n (%)	Observed events, n (%)	Absolute difference	Discordance (%)[a]	c-statistic
Women	3388	298.1 (8.80)	149 (4.40)	4.40	100	0.74
White	1286	97.9 (7.61)	57 (4.43)	3.18	72	0.70
Black	979	108.4 (11.07)	50 (5.11)	5.96	117	0.75
Chinese	392	31.7 (8.07)	9 (2.30)	5.78	252	0.83
Hispanic	731	60.2 (8.24)	33 (4.51)	3.72	82	0.79
Men	3053	425.0 (13.92)	220 (7.21)	6.71	93	0.71
White	1194	161.1 (13.49)	85 (7.12)	6.37	90	0.71
Black	798	117.2 (14.69)	65 (8.15)	6.54	80	0.68
Chinese	371	49.7 (13.38)	12 (3.23)	10.15	314	0.63
Hispanic	690	97.0 (14.06)	58 (8.41)	5.66	67	0.75

[a]Discordance is defined as ([{expected percentage − observed percentage}/observed percentage] × 100).

Table 3 Atherosclerotic cardiovascular disease events predicted via the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score and atherosclerotic cardiovascular disease events observed among Multi-Ethnic Study of Atherosclerosis participants aged 45–79, not taking lipid-lowering medication at baseline with low-density lipoprotein cholesterol between 70 and 189 mg/dL stratified by gender and race/ethnicity

Risk score	n	Predicted events, n (%)	Observed events, n (%)	Absolute difference	Discordance (%)[a]	c-statistic
Women	2629	211.3 (8.04)	113 (4.30)	3.74	87	0.75
White	1003	69.7 (6.94)	40 (3.99)	2.96	74	0.70
Black	744	77.5 (10.41)	38 (5.11)	5.30	104	0.75
Chinese	308	22.6 (7.34)	7 (2.27)	5.07	223	[b]
Hispanic	574	41.6 (7.24)	28 (4.88)	2.36	49	0.81
Men	2387	317.1 (13.28)	164 (6.87)	6.41	93	0.71
White	900	118.3 (13.14)	68 (7.56)	5.59	74	0.71
Black	614	86.2 (14.05)	44 (7.17)	6.88	96	0.70
Chinese	315	40.7 (12.91)	10 (3.17)	9.73	307	[b]
Hispanic	558	71.9 (12.89)	42 (7.53)	5.36	71	0.74

[a]Discordance is defined as ([{expected percentage − observed percentage}/observed percentage] × 100).
[b]Too few events for this statistic.

Table 4 Atherosclerotic cardiovascular disease events predicted via the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score and atherosclerotic cardiovascular disease events observed among Multi-Ethnic Study of Atherosclerosis participants aged 45–79, not taking lipid-lowering medication at baseline with low-density lipoprotein cholesterol between 70 and 189 mg/dL stratified by gender and race/ethnicity, including non-adjudicated Centers for Medicare & Medicaid Services myocardial infarctions

Risk score	n	Predicted events, n (%)	Observed events, n (%)	Absolute difference	Discordance (%)[a]	c-statistic
Women	2629	211.3 (8.04)	118 (4.49)	3.55	79	0.77
White	1003	69.7 (6.94)	40 (3.99)	2.96	74	0.70
Black	744	77.5 (10.41)	39 (5.24)	5.17	99	0.77
Chinese	308	22.6 (7.34)	8 (2.60)	4.74	183	[b]
Hispanic	574	41.6 (7.24)	31 (5.40)	1.84	34	0.84
Men	2387	317.1 (13.28)	174 (7.29)	6.00	82	0.71
White	900	118.3 (13.14)	72 (8.00)	5.14	64	0.72
Black	614	86.2 (14.05)	45 (7.33)	6.72	92	0.70
Chinese	315	40.7 (12.91)	12 (3.81)	9.10	239	[b]
Hispanic	558	71.9 (12.89)	45 (8.06)	4.83	60	0.74

[a]Discordance is defined as ([{expected percentage − observed percentage}/observed percentage] × 100).
[b]Too few events for this statistic.

respect to impact of ASCVD risk factors on event rates were undetectable in MESA. While this finding may be limited by sample size, it is clear that the effect size, if any exists, is not large enough to be detected in the MESA cohort. Not surprisingly, modelling the interaction between race and each of the risk factors also did not suggest significant differences between White and Black individuals (Supplementary material online, *Table S3*).

Estimating the AHA-ACC-ASCVD Cox model in MESA yields very different coefficients for the same constituent risk factor variables (Supplementary material online, *Tables S4* and *S5*). This is in contrast to the more similar coefficients for estimating the Reynolds or NCEP-ATPIII risk scores via Cox models in MESA (Supplementary material online, *Table S6*). These findings suggest that the relationship of risk factors used in the AHA-ACC-ASCVD risk score has a different relationship to ASCVD events in the AHA-ACC-ASCVD derivation cohort than in MESA. Modelling of the AHA-ACC-ASCVD risk score in MESA demonstrates a mean absolute risk overestimation of 5.5% ($P < 0.001$) (*Table 5*). Importantly, this corrects to a non-significant 0.34% reference group underestimation ($P = 0.87$) in a multivariable-adjusted model. The magnitude of model overestimation is not directly comparable; however, the fact that the multivariable model estimate (0.34%) is not statistically significantly different from zero indicates that the risk factors included in this model account for the overestimation observed with the AHA-ACC-ASCVD risk score in MESA. In this analysis, male gender, higher age, Black and Chinese race/ethnicity (when compared with White), systolic blood pressure (treated and untreated), diabetes, exercise, anti-hypertensive, lipid-lowering therapy, and aspirin therapy use were all associated with risk overestimation in the single-variable analysis (*Figures 1–3* and *Table 5*). Significance was lost for male gender ($P = 0.051$), Black race/ethnicity, and anti-hypertensive therapy and gained for alcohol use in the multivariable-adjusted model (*Table 5*). For example, after

holding all other factors in our model constant, each decade increase in age was associated with a mean 3.7% greater absolute risk overestimation. Factors examined that were not associated with risk overestimation in the multivariable-adjusted model included male gender, Black and Hispanic race/ethnicity, total cholesterol, HDL cholesterol, smoking status, body mass index, diet, education level, income, anti-hypertensive medication, and interim revascularization. Family history of heart attack was associated with less overestimation in both models. A sensitivity analysis limited to MESA participants that met clinical criteria consistent with guideline recommendations for the use of the AHA-ACC-ASCVD risk score to guide statin therapy was similar to the primary analysis with the exception that alcohol use and exercise were no longer significant predictors of discordance in the multivariable-adjusted model (Supplementary material online, *Table S7*). Including 20 unadjudicated CMS MIs as ASCVD events did not meaningfully change the overall results of these analyses (Supplementary material online, *Tables S8* and *S9*).

Discussion

The MESA cohort appears to be a valid representation of a modern day US-based primary prevention population as demonstrated by similar baseline mean risk factor measures, the distribution of subjects in four clinically relevant risk categories, and by similar treatment rates when compared with a representative sample of ASCVD-free, non-pregnant US adults (NHANES). The AHA-ACC-ASCVD risk score overestimates risk in men, women, and all four race/ethnic groups studied in MESA—including White and Black Americans for whom the risk score is specifically recommended. Consistent with the age-matched peers considered representative of the general American primary prevention population, ~20% of MESA subjects were on lipid-lowering therapy at baseline. However, results were essentially

Table 5 Absolute risk regression (generalized linear model assuming Gaussian error distribution with robust standard errors) to evaluate the impact of a single risk factor (β-coefficient) while adjusting for all the other risk factors in the model

Risk factor	Single variable			Multivariable		
	Coef.	(95% CI)	P	Coef.	(95% CI)	P
Intercept	5.5	(4.92 to 6.07)	<0.001	−0.34	(−3.77 to 4.44)	0.873
Male	2.31	(1.15 to 3.48)	<0.001	1.28	(−0.01 to 2.57)	0.051
Age, per 10 years	4.9	(4.29 to 5.5)	<0.001	3.73	(3.03 to 4.43)	<0.001
Race/ethnicity						
Black	1.51	(0.02 to 2.99)	0.047	1.42	(−0.18 to 3.02)	0.082
Chinese	3.19	(1.57 to 4.81)	<0.001	4.07	(2.23 to 5.92)	<0.001
Hispanic	−0.05	(−1.61 to 1.51)	0.946	1.26	(−0.62 to 3.14)	0.189
SBP, per 10 mmHg						
Untreated	1.13	(0.78 to 1.47)	<0.001	0.62	(0.24 to 0.99)	0.001
Treated	1.37	(1.06 to 1.68)	<0.001	0.66	(0.29 to 1.04)	0.001
Total cholesterol, per 10 mg/dL	−0.07	(−0.24 to 0.09)	0.373	−0.03	(−0.2 to 0.14)	0.732
HDL, per 10 mg/dL	−0.14	(−0.52 to 0.23)	0.457	−0.04	(−0.48 to 0.4)	0.862
Diabetes	7.08	(4.63 to 9.54)	<0.001	4.21	(1.72 to 6.69)	0.001
Current smoker	−1.96	(−3.95 to 0.04)	0.054	0.24	(−1.75 to 2.23)	0.814
Alcohol user	0.23	(−0.95 to 1.4)	0.705	1.46	(0.20 to 2.72)	0.023
Body mass index	−0.08	(−0.18 to 0.02)	0.14	−0.09	(−0.21 to 0.04)	0.167
Unhealthy diet	−0.17	(−1.38 to 1.04)	0.781	0.00	(−1.24 to 1.24)	0.998
Exercise, per 100 met/min/day	0.03	(0.00 to 0.05)	0.022	0.02	(0.00 to 0.04)	0.026
Education						
<High school	1.59	(−0.13 to 3.31)	0.07	−0.07	(−1.91 to 1.76)	0.939
Bachelor's	0.54	(−0.95 to 2.02)	0.477	0.94	(−0.59 to 2.46)	0.227
Graduate/Prof.	0.6	(−0.89 to 2.1)	0.429	0.62	(−0.91 to 2.2)	0.446
Income, per $10k	−0.13	(−0.29 to 0.02)	0.1	0.12	(−0.06 to 0.31)	0.197
Family history	−2.48	(−3.74 to −1.22)	<0.001	−2.40	(−3.66 to −1.13)	<0.001
Treatment						
Anti-hypertensive	5.92	(4.81 to 7.03)	<0.001	0.93	(−0.53 to 2.39)	0.213
Lipid-lowering	5.68	(4.53 to 6.83)	<0.001	3.17	(1.85 to 4.48)	<0.001
Aspirin	5.58	(4.43 to 6.73)	<0.001	3.03	(1.78 to 4.27)	<0.001
Revascularization	2.9	(−1.42 to 7.21)	0.189	−2.15	(−6.4 to 2.11)	0.323

Coef, coefficient [absolute percentage (risk score points)]; CI, confidence interval; HDL, high-density lipoprotein cholesterol; SBP, systolic blood pressure.
Positive values represent absolute value that AHA-ACC-ASCVD risk score overestimated risk in this model (n = 6441).
Coefficients represent absolute percentage (risk score points) contributed by each variable to the difference between observed and AHA-ACC-ASCVD predicted ASCVD events. Positive values represent overestimation, whereas negative values represent underestimation. Bold text indicates that P-values were statistically significant at the P < 0.05 level. Absolute risk model is a linear regression model at the individual level, predicting a dichotomous outcome (ASCVD event yes/no within 10 years). It was fit as a generalized linear model with the AHA-ACC-ASCVD risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors. Continuous variables are mean-centred. Missing data for diet (n = 259, 4%), income (n = 222, 3%), exercise (n = 2), and education (n = 1) were handled using multiple imputation with sequential chained regression and 10 imputed datasets; Rubin's rules were used to combine the standard errors.[24] Reference category for race/ethnicity is white. Unhealthy diet has been described and validated previously.[25] Exercise is total intentional physical exercise. Reference category for education is high school graduate. Treatment was measured during follow-up visits and indicates that participant ever received treatment. In an effort to study revascularizations that may have prevented subsequent events, all revascularizations >5 days prior to an event, or revascularizations not followed by any event, were selected for modelling.

unchanged in a sensitivity analysis that included only MESA participants that met clinical criteria consistent with guideline recommendations for the use of the AHA-ACC-ASCVD risk score to guide statin therapy (not taking lipid-lowering medication at baseline and having an LDL-C between 70 and 189 mg/dL). This and previous data from MESA and other cohorts demonstrate that a large proportion of risk overestimation with the AHA-ACC-ASCVD risk score is not explained by the use of lipid-lowering therapy.[5,9,20] In fact, a sensitivity analysis excluding MESA subjects treated with aspirin, lipid-lowering, anti-hypertensive medication at baseline or at any of the five follow-up visits or interim coronary revascularization failed to provide evidence that these treatments explain overestimation by the AHA-ACC-ASCVD risk score.[9] Prior work demonstrates overestimation throughout the continuum of low to high risk by the AHA-ACC-ASCVD score and specifically in those individuals with a calculated AHA-ACC-ASCVD risk of 7.5–10% (just over the guideline-recommended risk threshold of 7.5% for consideration of stain therapy).[9]
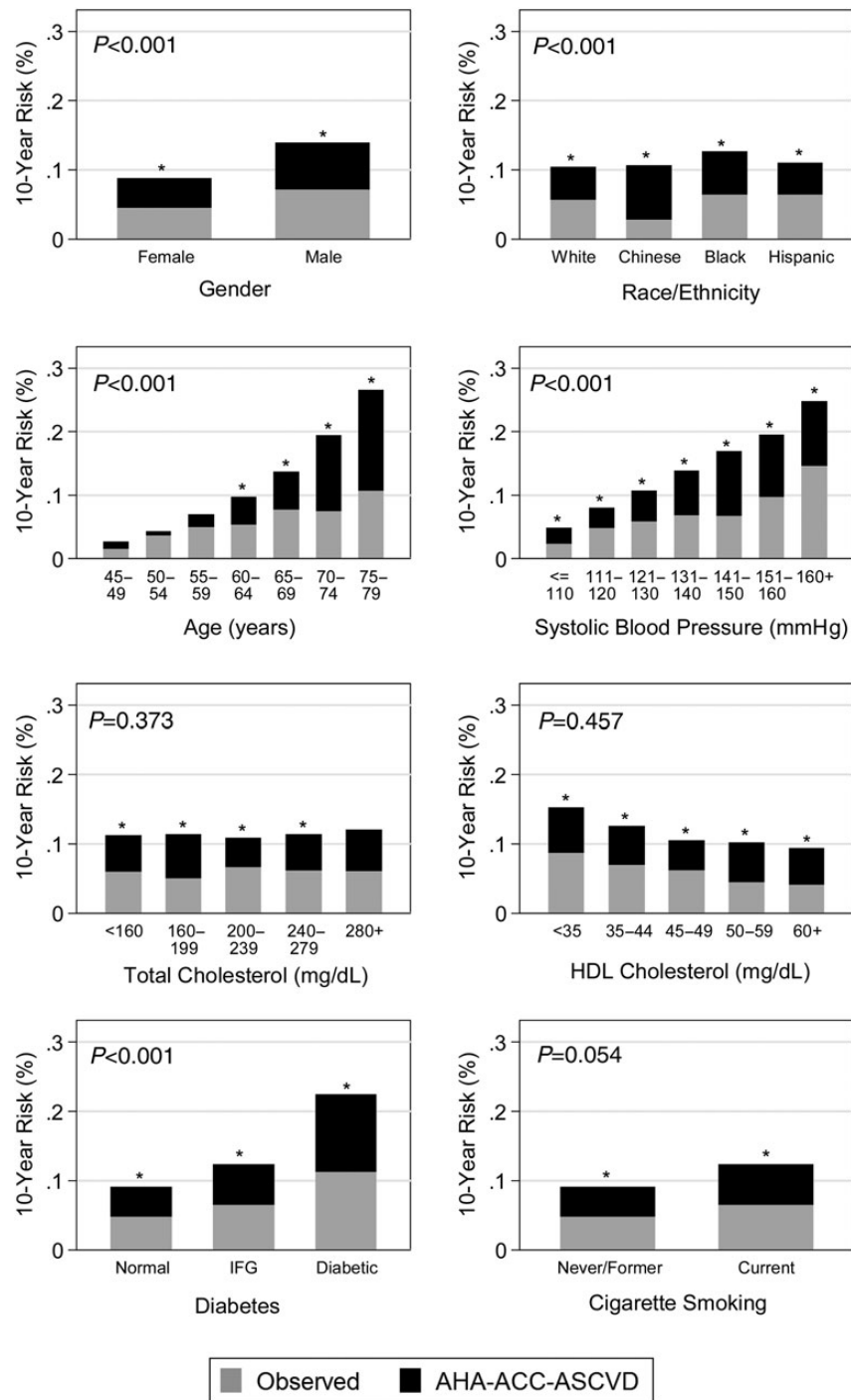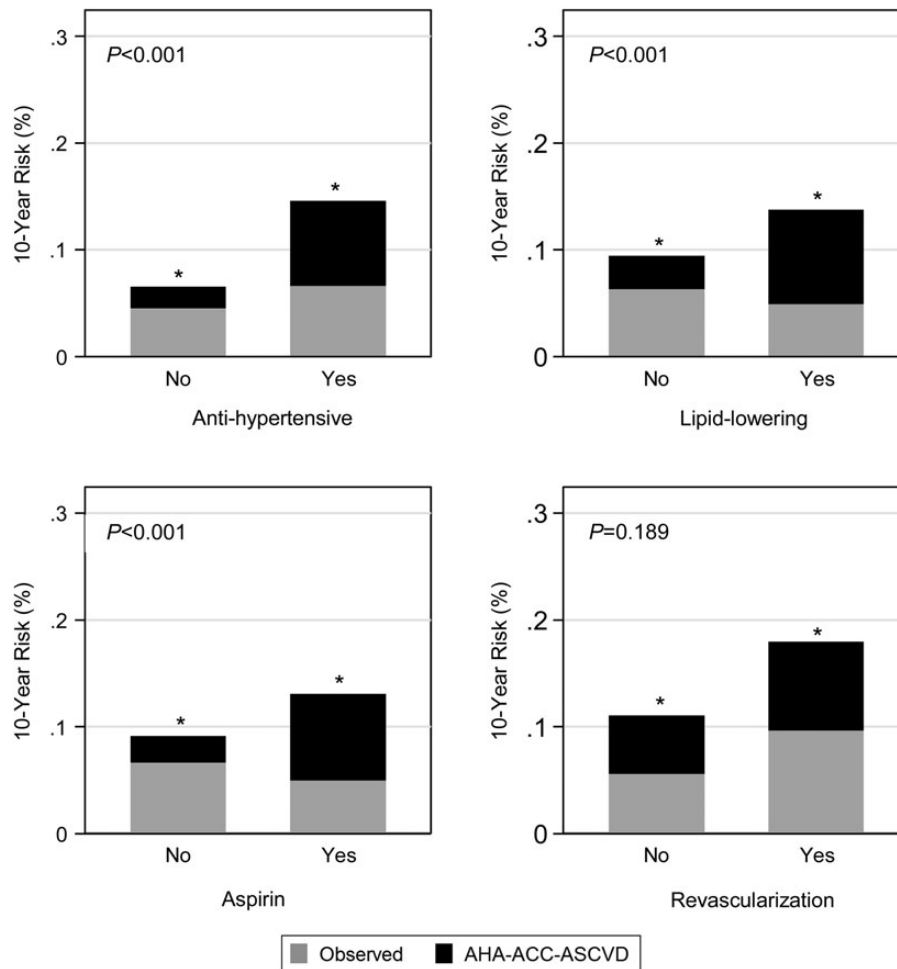
Figure 1 Observed atherosclerotic cardiovascular disease percentage and American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score predicted percentage. *P*-value of <0.05 for proportion test comparing American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) with the observed risk in Multi-Ethnic Study of Atherosclerosis (grey portion of bars). For example, the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk for men was 13.9%, whereas the observed rate was 7.2%, and a two-tailed test of proportions showed these rates were significantly different at the 95% level. Reported *P*-value compares the overestimation (i.e. the black bars) for each risk factor. For example, the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) was higher than the observed risk (grey portion of the bar) for females and for males, and the overestimation for males was significantly greater (*P* < 0.001) than the overestimation for females. *P*-values come from an absolute risk regression model, which is a linear regression model at the individual level, predicting a dichotomous outcome (atherosclerotic cardiovascular disease event yes/no within 10 years). It was fit as a generalized linear model with the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors. To this model, we added each risk factor separately. *P*-value for race/ethnicity categories shows joint *F*-test of significance.
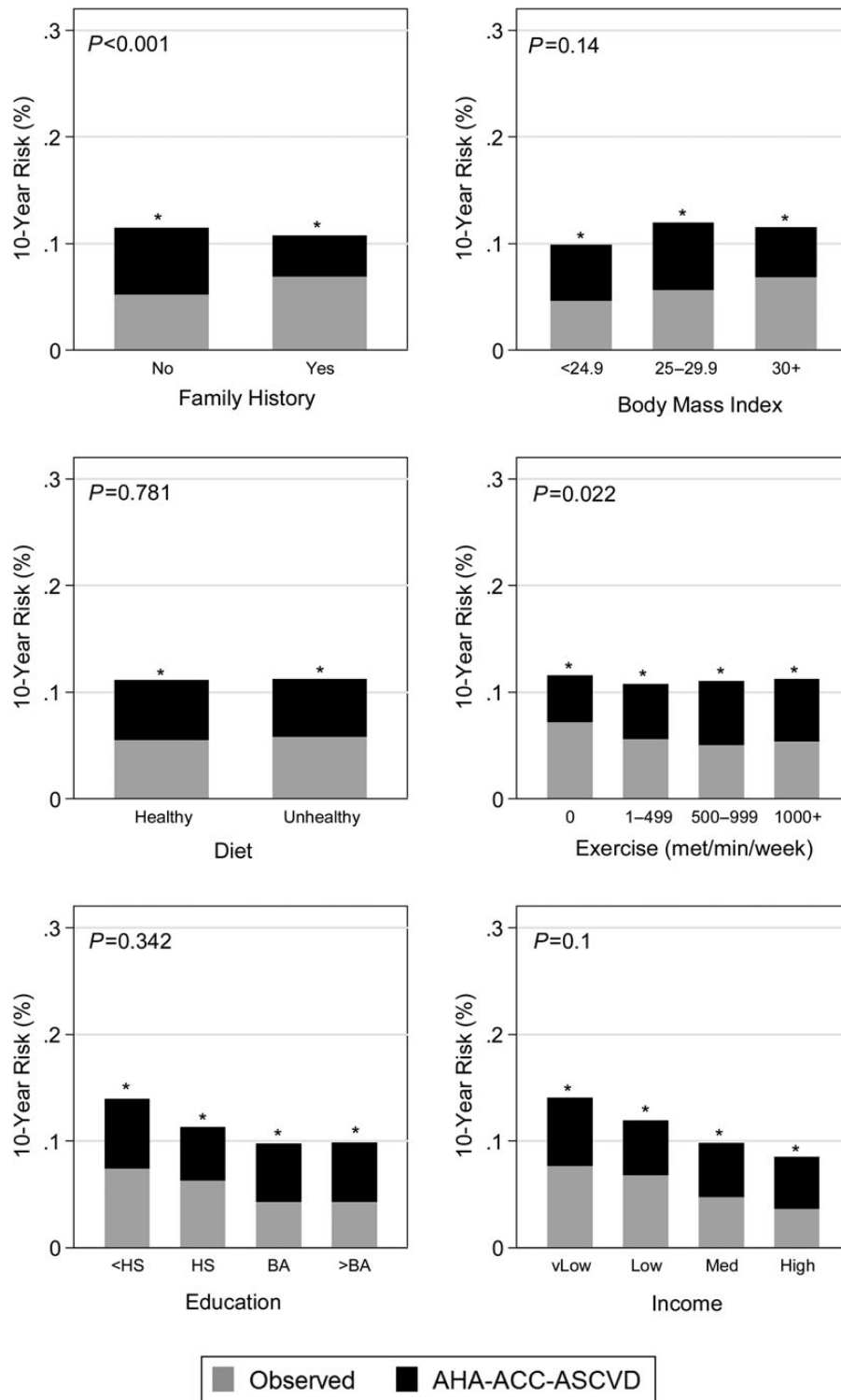
Figure 2 Observed atherosclerotic cardiovascular disease percentage and American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score predicted percentage among factors not included in the risk score. *P-value of <0.05 for proportion test comparing American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) with the observed risk in Multi-Ethnic Study of Atherosclerosis (grey portion of bars). Reported P-value compares the overestimation (i.e. the black bars) for each risk factor. P-values come from an absolute risk regression model, which is a linear regression model at the individual level, predicting a dichotomous outcome (atherosclerotic cardiovascular disease event yes/no within 10 years). It was fit as a generalized linear model with the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors. To this model, we added each risk factor separately. P-value for education categories variables shows joint F-test of significance.

Figure 3 Observed atherosclerotic cardiovascular disease percentage and American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score predicted percentage by time-updated treatments. *P-value of <0.05 for proportion test comparing American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) with the observed risk in Multi-Ethnic Study of Atherosclerosis (grey portion of bars). Reported P-value compares the overestimation (i.e. the black bars) for each risk factor. P-values come from an absolute risk regression model, which is a linear regression model at the individual level, predicting a dichotomous outcome (atherosclerotic cardiovascular disease event yes/no within 10 years). It was fit as a generalized linear model with the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors. To this model, we added each risk factor separately.

The events collection and adjudication process for MESA is robust and included successfully obtaining medical records for ~98% of reported hospitalized CHD and CVD events and information on 95% of reported outpatient cardiovascular diagnostic encounters. Follow-up telephone interviews were completed in 92% of living participants. In comparison, in the Framingham study, one of the studies used to derive the AHA-ACC-ASCVD risk score, events were captured using a combination of self-reporting, medical record review, contact with patients' personal physicians, and examinations in the Framingham Clinic.[21] Despite the rigour of event capture employed in MESA, an evaluation of the CMS database identified 20 MIs not adjudicated as events in MESA. Given the methodology for capturing clinical events in MESA appears to be similar to that of the studies used to derive the AHA-ACC-ASCVD risk score, it is unlikely that MESA has missed significantly more events than that missed in the AHA-ACC-ASCVD risk score derivation cohort. Given the small number of events missed, it is unlikely that missed events explain a substantial fraction of risk overestimation. This conclusion is supported by our sensitivity analyses, which includes the addition of 20 MIs identified in the CMS database, but not adjudicated as ASCVD events in MESA, which did not significantly change the results of this study.

We demonstrated that the relationships between risk factors used in the AHA-ACC-ASCVD risk score and ASCVD events are different in the AHA-ACC-ASCVD derivation cohort than in MESA by demonstrating significantly different coefficients when

estimating the AHA-ACC-ASCVD Cox model in MESA. Additional evidence of poor risk factor calibration is evident in our generalized linear modelling that implicated several factors in the AHA-ACC-ASCVD risk score: older age, systolic blood pressure (treated and untreated), and diabetes status, as contributors to overestimation in the MESA cohort. Our modelling also identified other factors not currently part of the AHA-ACC-ASCVD risk score that were associated with AHA-ACC-ASCVD risk score overestimation in MESA: Chinese race/ethnicity, alcohol use, exercise, aspirin therapy, and lipid-lowering medication. Presence of a family history of heart attack was associated with less overestimation of risk. These data are supportive of the notion that changing significance of risk factors from older cohorts, used to develop the AHA-ACC-ASCVD risk score, to the more modern MESA cohort may explain the poor performance of the AHA-ACC-ASCVD risk score in MESA.[9] For example, the treatment of diabetes has changed dramatically over the decades since the creation of the pooled cohorts used to develop the AHA-ACC-ASCVD risk score. The implications of being 70 years old on cardiovascular risk is likely different now than it was decades ago.[22] Treatment with anti-hypertensive, lipid-lowering, or aspirin therapy was associated with risk overestimation in our unadjusted model. Although attenuated, lipid-lowering and aspirin therapies remained associated with risk overestimation in our multivariable model, whereas anti-hypertensive therapy, the only therapy considered in the AHA-ACC-ASCVD risk equation, was no longer predictive of risk overestimation. These findings suggest that the inclusion of additional treatment variables, such as lipid-lowering and/or aspirin therapy, may improve risk prediction and therefore should be considered in future risk score development.

More than half of the growth in the total population of the USA between 2000 and 2010 was due to the increase in the Hispanic population, and the number of Asian Americans has increased by over 40% in this same time interval.[23] The need for an accurate risk assessment tool in these growing American populations is clear. We found no evidence to suggest that risk factors affect ASCVD risk differently in Black vs. White individuals and calibration of the AHA-ACC-ASCVD risk score is poor in all races examined in MESA. The need for better risk prediction among all races is clear, but the need for individual race-based risk assessment algorithms is not clear from our analysis in MESA and therefore requires further investigation.

In conclusion, MESA appears representative of a modern day US-based primary prevention population. The AHA-ACC-ASCVD risk score overestimation is observed in men, women, and the four race/ethnic groups evaluated in MESA—including White and Black men and women for whom the new risk score is specifically recommended. Clinicians may need to interpret AHA-ACC-ASCVD risk estimates with caution, especially among older individuals, Chinese Americans, and those with hypertension or diabetes. Risk prediction is an evolving science and will require continual updating through the study of well-characterized, contemporary primary prevention cohorts.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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