JAMA Cardiology | Original Investigation

Cardiovascular Disease Risk Assessment Using Traditional Risk Factors and Polygenic Risk Scores in the Million Veteran Program

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IMPORTANCE Primary prevention of atherosclerotic cardiovascular disease (ASCVD) relies on risk stratification. Genome-wide polygenic risk scores (PRSs) are proposed to improve ASCVD risk estimation.

OBJECTIVE To determine whether genome-wide PRSs for coronary artery disease (CAD) and acute ischemic stroke improve ASCVD risk estimation with traditional clinical risk factors in an ancestrally diverse midlife population.

DESIGN, SETTING, AND PARTICIPANTS This was a prognostic analysis of incident events in a retrospectively defined longitudinal cohort conducted from January 1, 2011, to December 31, 2018. Included in the study were adults free of ASCVD and statin naive at baseline from the Million Veteran Program (MVP), a mega biobank with genetic, survey, and electronic health record data from a large US health care system. Data were analyzed from March 15, 2021, to January 5, 2023.

EXPOSURES PRSs for CAD and ischemic stroke derived from cohorts of largely European descent and risk factors, including age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, and diabetes status.

MAIN OUTCOMES AND MEASURES Incident nonfatal myocardial infarction (MI), ischemic stroke, ASCVD death, and composite ASCVD events.

RESULTS A total of 79 151 participants (mean [SD] age, 57.8 [13.7] years; 68 503 male [86.5%]) were included in the study. The cohort included participants from the following harmonized genetic ancestry and race and ethnicity categories: 18 505 non-Hispanic Black (23.4%), 6785 Hispanic (8.6%), and 53 861 non-Hispanic White (68.0%) with a median (5th-95th percentile) follow-up of 4.3 (0.7-6.9) years. From 2011 to 2018, 3186 MIs (4.0%), 1933 ischemic strokes (2.4%), 867 ASCVD deaths (1.1%), and 5485 composite ASCVD events (6.9%) were observed. CAD PRS was associated with incident MI in non-Hispanic Black (hazard ratio [HR], 1.10; 95% CI, 1.02-1.19), Hispanic (HR, 1.26; 95% CI, 1.09-1.46), and non-Hispanic White (HR, 1.23; 95% CI, 1.18-1.29) participants. Stroke PRS was associated with incident stroke in non-Hispanic White participants (HR, 1.15; 95% CI, 1.08-1.21). A combined CAD plus stroke PRS was associated with ASCVD deaths among non-Hispanic Black (HR, 1.19; 95% CI, 1.03-1.17) and non-Hispanic (HR, 1.11; 95% CI, 1.03-1.21) participants. The combined PRS was also associated with composite ASCVD across all ancestry groups but greater among non-Hispanic White (HR, 1.20; 95% CI, 1.16-1.24) than non-Hispanic Black (HR, 1.11; 95% CI, 1.05-1.17) and Hispanic (HR, 1.12; 95% CI, 1.00-1.25) participants. Net reclassification improvement from adding PRS to a traditional risk model was modest for the intermediate risk group for composite CVD among men (5-year risk >3.75%, 0.38%; 95% CI, 0.07%-0.68%), among women, (6.79%; 95% CI, 3.01%-10.58%), for age older than 55 years (0.25%; 95% CI, 0.03%-0.47%), and for ages 40 to 55 years (1.61%; 95% CI, −0.07% to 3.30%).

CONCLUSIONS AND RELEVANCE Study results suggest that PRSs derived predominantly in European samples were statistically significantly associated with ASCVD in the multiancestry midlife and older-age MVP cohort. Overall, modest improvement in discrimination metrics were observed with addition of PRSs to traditional risk factors with greater magnitude in women and younger age groups.

JAMA Cardiol. doi:10.1001/jamacardio.2023.0857
Published online May 3, 2023.

Supplemental content

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Atherosclerotic cardiovascular disease (ASCVD) is a tremendous source of morbidity and mortality globally.[1] Primary prevention with statin and aspirin therapy can significantly decrease this burden; however, estimating patient risk is a key first step to identifying patients who would benefit. Despite improvements in the last decade, current clinical prediction models misclassify a considerable number of individuals, resulting in overtreatment or undertreatment of ASCVD risk.[2,3]

Polygenic risk scores (PRSs) have been proposed to improve CVD risk stratification. Advances in statistical methods, computational capability, and the size of genome-wide association studies (GWASs) for discovery have improved the performance of PRSs in discriminating disease cases from controls and estimating risk of incident disease. Specifically, significant advances have occurred in the development and validation of PRSs for coronary artery disease (CAD), including their extension into populations of diverse genetic ancestry.[4,5] Research and clinical efforts are now underway to evaluate the utility of PRSs in patient risk stratification and disease prevention.[6-8] The advent of genetic research and promulgation of polygenic risk analyses across the globe has added a new perspective to CVD prevention.[9-11]

In current clinical practice in the US, standard of care includes using a risk calculator to estimate a patient's absolute risk for ASCVD, a composite outcome including CAD events (nonfatal myocardial infarction, coronary heart disease death), and fatal or nonfatal stroke. Prior research has demonstrated that PRSs derived from CAD GWAS data may modestly improve the risk estimation achieved by clinical risk prediction models such as the Pooled Cohort Equations.[2,12] However, few studies have examined how leveraging GWAS data from multiple ASCVD phenotypes, namely CAD and acute ischemic stroke, contributes to ASCVD risk estimation through the addition of PRSs and whether the degree of improvement in risk prediction varies by ancestry.[4]

The hypothesis tested was that incorporating PRSs for both CAD and ischemic stroke into a clinical ASCVD risk model improves risk estimation compared with the clinical model alone. Data were analyzed from the Million Veteran Program (MVP) within the Veterans Health Administration (VHA). The MVP is a large, national, ancestrally diverse longitudinal cohort study with genetic, survey, and electronic medical record data.[13] First, previously published CAD and ischemic stroke PRSs derived from cohorts of largely European descent were assessed for their ability to predict individual and composite ASCVD outcomes in a multiancestry population. Second, the performance for predicting ASCVD events from traditional risk factor models was compared against PRS models and models including both traditional risk factors and PRSs.

Key Points

Question Do polygenic risk scores (PRSs) for coronary heart disease and acute ischemic stroke predict incident atherosclerotic cardiovascular disease (ASCVD) events?

Findings In an ancestrally diverse, primary prevention sample of almost 80 000 veterans observed for up to 7 years, PRSs were significantly associated with incident myocardial infarction, acute ischemic stroke, and cardiovascular death. Discrimination was modest overall but greater among women and younger participants.

Meaning PRSs provide modest incremental benefit for ASCVD risk stratification in a general midlife and older age population over and above traditional risk factors.

Methods

Study Population

This prognostic study was approved by the VA Central Institutional Review Board. All participants provided written informed consent. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines were followed.

The study sample was drawn from MVP participants who were genotyped and had at least 1 outpatient lipid measurement in the year before enrollment. To create a primary ASCVD prevention cohort, patients were excluded for history of myocardial infarction (MI), revascularization, ischemic stroke, or statin use at baseline.[14] Additionally, participants with serious comorbid conditions were excluded because a traditional ASCVD risk model would inadequately estimate risk in these patient populations; these conditions included HIV positivity, chronic kidney disease, liver disease or hepatitis, cancer (other than nonmelanoma skin cancer), schizophrenia, dementia, and amputation.[14] Participants were categorized into harmonized ancestry and race and ethnicity (HARE) groups. As described previously, the HARE algorithm uses a machine learning model to predict self-identified race and ethnicity (SIRE) from principal components of genetic ancestry and was developed to facilitate ancestry-specific GWAS in the MVP.[15] The HARE algorithm was trained on SIRE groups based on participant responses to the MVP baseline survey questions "Are you Spanish, Hispanic, or Latino?" and "What is your race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or other)?" HARE was defined for the 4 largest race and ethnicity groups: non-Hispanic Asian, non-Hispanic Black, Hispanic, and non-Hispanic White (abbreviated as Asian, Black, Hispanic, and White, respectively). The Asian group was excluded in the present analyses due to limited ASCVD data (<100 incident events). Although SIRE was previously used to train the HARE algorithm, it was not used in these analyses. Agreement between HARE and genetically informed ancestry (GIA) classification was very high for all ancestries except the Admixed American ancestry (ie, continental American populations with different global proportions of European, Native American, and Sub-Saharan African ancestry), among whom 10% were classified by HARE as non-Hispanic White, and 90% were classified as Hispanic (eTable 1 in Supplement 1). This degree of overlap reflects recent admixture among Native American, European and African ancestral populations and is appropriate for ASCVD risk estimation.[16] Given the

high degree of concordance between HARE and GIA, no separate analyses were performed for GIA. Patient follow-up extended from MVP enrollment in January 1, 2011, until December 31, 2018.

Data Sources

Electronic health records were extracted from the national VA Corporate Data Warehouse.[17] Outcomes ascertained in the VHA were supplemented with records from the Centers for Medicaid & Medicare Services (CMS) and National Death Index databases.[18,19] Genetic variants in MVP were genotyped with an Applied Biosystems (formerly Affymetrix) microarray (Thermo Fisher Scientific).[20]

PRSs

Primary analyses used PRSs for ischemic stroke[21] and CAD,[22] which combined GWAS associations from European and non-European ancestries but were optimized in European cohorts. Sensitivity analyses in young adults (age <40 years) were conducted with PRSs from the UK Biobank (UKBB) for ischemic stroke and CAD[23] to better match previous UK studies of age-related PRS trends. For variants not genotyped in MVP, dosages were imputed using the 1000 Genomes Project reference panel[24] and African Genome Resources panel.[25]

Other Risk Factors

Patient characteristics were assessed at baseline, which was an outpatient VA clinic visit close to MVP enrollment date. Baseline diabetes status was defined as outpatient hemoglobin A_{1c} level of at least 6.5% or any prescription for diabetes medication before enrollment plus 1 *International Classification of Diseases, Ninth Revision* (*ICD-9*) 250.xx (or equivalent *Tenth Revision* [*ICD-10*]) code in combination with a VA primary care visit or at least 2 total *ICD* codes. Smoking status (current, former, never) was ascertained from smoking-related health factors and *ICD-9* codes for tobacco dependence using an algorithm previously validated in the VA.[26] Statin therapy and antihypertensive therapy were defined as an active prescription for a relevant medication on the baseline date.[14] Continuous clinical measures were averaged over all outpatient measures recorded in the preceding year. Medications and *ICD* codes used for inclusion/exclusion are available in a previous publication.[14]

Outcomes

Incident ischemic stroke and MI events were defined as the first occurrences of *ICD-9*, *ICD-10*, or CMS codes used by phenotyping algorithms that had been validated with expert medical record review in the VA.[14,27,28] Incident ischemic stroke *ICD* codes included 433.x1, 434 (excluding 434.x0), 436, 437.0, 437.6, I63.xx9, I63.20, I63.22, I63.30, I63.40, I63.50, I63.59, I67.2, I67.6, and I67.89. Incident MI *ICD* codes included 410, 411.0, I21, and I22. ASCVD death was defined as any of the following *ICD-10-Clinical Modification* diagnosis codes as the primary cause of death in the National Death Index: I10, I11, I13, I16, I20 to I25, I46, I63, I67, I70, I74, I75, and G45.[14] Composite ASCVD events included first occurrence of ischemic stroke, MI, or ASCVD death. Revascularization was defined as any percutaneous coronary intervention and coronary artery bypass graft (eTable 2 in Supplement 1). Follow-up time for each ASCVD outcome began at MVP enrollment date and ended at date of first outcome, death, or administrative censoring (December 31, 2018).[29]

Statistical Analysis

Cox proportional hazard models were used to estimate the risk of incident ASCVD events, using separate models for composite ASCVD and each component outcome of ASCVD events (ischemic stroke, MI, or ASCVD death), stratified by HARE group. Sex-stratified models were also estimated for composite ASCVD. Complete case analysis was used for all models, only including patients with nonmissing risk factors. Polygenic scores were validated in ancestry-specific models with standardized PRSs for each outcome, age, sex, and the first 5 principal components of genetic ancestry (G model):

$$\log[h(t) / h_O(t)] = \beta_1\text{age} + \beta_2\text{female} + \beta_{3\text{-}7}PCs\ 1\text{-}5 + \beta^T{}_G\text{PRS},$$

where $h(t)$ is the hazard for an outcome (composite ASCVD events, stroke, MI, or ASCVD death), $h_O(t)$ is the baseline hazard, PCs are principal components, and composite polygenic score (G-score) is $\beta^T{}_G\text{PRS} = \beta_8 PRS_{AIS} + \beta_9 PRS_{CAD}$ for composite ASCVD events and ASCVD death, $\beta_8 PRS_{AIS}$ for stroke, and $\beta_8 PRS_{CAD}$ for MI. Traditional risk scores were constructed using nongenetic risk factors (E model) from a previously developed VHA model[14]:

$$\log[h(t) / h_O(t)] = \beta_1\text{Age} + \beta_2\text{female} + \beta_3\text{diabetes} + \beta_4\text{current smoker} + \beta_5\text{former smoker} + \beta_{6\text{-}8}\text{ total cholesterol(cubic splines)} + \beta_9\text{HDL-C} + \beta_{10}\text{SBP} + \beta_{11}\text{BP med Rx}.$$

Models were estimated in 10-fold cross-validation, with coefficients estimated on training samples, and traditional risk scores (E scores) and composite polygenic scores (G scores) computed for patients in validation folds.

A combined genetic and traditional risk (G × E) model was constructed to evaluate whether polygenic scores improved ASCVD risk prediction over and above traditional risk factors:

$$\log[h_{G\times E}(t) / h_O(t)] = \beta_E\text{E score} + \beta_G\text{G score} + \beta_{G\times E}\text{E score} \times \text{G score},$$

where E score and G score were combined across the 10 validation folds. This iterative approach to model building is similar to the approach of Steinfeldt et al,[30] with their Cox clinical model corresponding to the E model here, Cox Sun PGS model equivalent to the G model, and Cox clinical PGS × age equivalent to our G × E model (just with PRS by age instead of PRS and traditional risk).

Discrimination of the risk models was evaluated using the Harrell C index, with improvement from PRS defined as the difference between genetic and nongenetic models ($\Delta C = C_{G\times E} - C_E$). Categorical and continuous net reclassification improvement (NRI) were used to assess improvements in risk prediction from addition of PRS.[31] To define 5-year risk categories analogous to the guideline-recommended risk categories,[32] the primary 10-year risk threshold was halved to define intermediate-risk (3.75% to 10%) and high-risk (>10%) groups.

Table 1. Baseline Characteristics and Atherosclerotic Cardiovascular Disease (ASCVD) Events Among 79 151 Veterans

Baseline characteristic	No. (%)			
		Harmonized ancestry, race, and ethnicity		
	Total cohort (N = 79 151)	Non-Hispanic Black (n = 18 505)	Hispanic (n = 6785)	Non-Hispanic White (n = 53 861)
Follow-up, median (5th-95th percentile), y	4.3 (0.7-6.9)	4.3 (0.7-6.9)	4.1 (0.6-6.8)	4.3 (0.6-6.9)
Age, mean (SD), y	57.8 (13.7)	55.4 (11.8)	52.6 (14.8)	59.3 (13.8)
Cardiovascular risk factors				
Sex				
Male	68 503 (86.5)	15 153 (81.9)	5871 (86.5)	47 479 (88.2)
Female	10 648 (13.5)	3352 (18.1)	914 (13.5)	6382 (11.8)
Total cholesterol, mean (SD), mg/dL	157.8 (40.6)	153.7 (40.0)	156.0 (41.5)	159.5 (40.6)
HDL-C, mean (SD), mg/dL	49.8 (17.0)	54.0 (18.1)	47.4 (15.0)	48.6 (16.6)
LDL-C, mean (SD), mg/dL	109.4 (33.3)	106.6 (33.1)	106.9 (35.0)	110.6 (33.1)
Systolic blood pressure, mean (SD), mm Hg	131.3 (13.4)	132.5 (13.7)	129.6 (13.1)	131.0 (13.3)
Current smoker	8435 (10.7)	2034 (11.0)	812 (12.0)	5589 (10.4)
Former smoker	47 670 (60.2)	10 578 (57.2)	3527 (52.0)	33 565 (62.3)
Diabetes	17 177 (21.7)	5173 (28.0)	1663 (24.5)	10 341 (19.2)
Medications				
Blood pressure treatment	36 673 (46.3)	9390 (50.7)	2723 (40.1)	24 560 (45.6)
No. of events (2011-2018)				
Composite CVD (%)	5485 (6.9)	1227 (6.6)	322 (4.7)	3936 (7.3)
Composite CVD and revascularization (%)	6628 (8.4)	1428 (7.7)	411 (6.1)	4789 (8.9)
ASCVD death (%)	867 (1.1)	189 (1.0)	52 (0.8)	626 (1.2)
Acute ischemic stroke (%)	1933 (2.4)	481 (2.6)	124 (1.8)	1328 (2.5)
Myocardial Infarction (%)	3186 (4.0)	677 (3.7)	182 (2.7)	2327 (4.3)
Crude incidence rate per 10 000 person-years (2011-2018)				
Composite CVD (95% CI)	177.7 (173.0-182.5)	168.1 (158.8-177.8)	124.7 (111.5-139.1)	187.5 (181.7-193.5)
Composite CVD and revascularization (95% CI)	216.6 (211.4-221.9)	196.8 (186.7-207.2)	160.5 (145.4-176.8)	230.4 (223.9-237.0)
ASCVD Death (95% CI)	27.0 (25.2-28.8)	24.9 (21.5-28.8)	19.6 (14.6-25.7)	28.6 (26.4-30.9)
Acute ischemic stroke (95% CI)	61.0 (58.3-63.8)	64.4 (58.8-70.4)	47.3 (39.3-56.4)	61.5 (58.2-64.9)
Myocardial infarction (95% CI)	100.9 (97.4-104.4)	90.7 (84.0-97.8)	69.4 (59.6-80.2)	108.2 (103.9-112.7)

Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259.

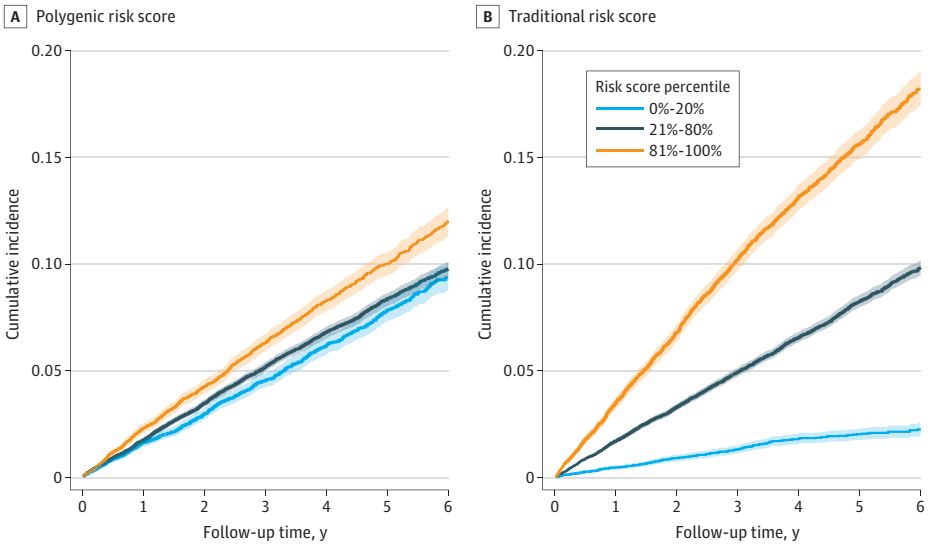
Kaplan-Meier incidence curves were stratified by low (bottom quintile of risk score), moderate (middle 3 quintiles), and high risk (top quintile) using ancestry-specific scores.[33] Cox regressions for high- and low-risk groups used a reference of 45th to 55th percentile of risk, adjusting for age, sex, and top 5 principal components of genetic ancestry in PRS models. Data were analyzed from March 15, 2021, to January 5, 2023, using R software, version 4.0.2 (R Foundation for Statistical Computing). Two-sided *P* values <.05 were considered statistically significant.

Results

The cohort comprised 79 151 veterans (mean [SD] age, 57.8 [13.7] years; 68 503 male [86.5%]; 10 648 female [13.5%]) without baseline ASCVD. As defined by HARE, veterans belonged to the following harmonized genetic ancestry and race and ethnicity categories: 18 505 Black (23.4%), 6785 Hispanic (8.6%), and 53 861 White (68.0%) (**Table 1** and eTable 3 in Supplement 1). Black and Hispanic participants were 6 to 10 years younger than White participants on average (mean [SD] age, Black, 53.2 [12.6] years; Hispanic, 49.4 [15.6] years; White, 59.3 [13.8] years). At baseline, 36 673 participants (46.3%) had active prescriptions for antihypertensive therapies, mean (SD) total cholesterol level was 157.8 (40.6) mg/dL (to convert to millimoles per liter, multiply by 0.0259), and prevalence of current smoking was 10.7% (8435), of former smoking was 60.2% (47 670), and of diabetes was 21.7% (17 177) (Table 1).

During follow-up (median [5th-95th percentile], 4.3 [0.7-6.9] years), 5485 participants (6.9%) experienced a first ASCVD event, among whom 3186 (4.0%) experienced an MI, 1933

Figure 1. Cumulative Incidence of Composite Atherosclerotic Cardiovascular Disease Events



Cumulative incidence curves for low (light blue line), moderate (dark blue line), and high (orange line) predicted polygenic (A) and traditional (B) risk are presented. Shaded regions are 95% exact Poisson CIs.

(2.4%) experienced an ischemic stroke, and 867 (1.1%) died of an ASCVD event, including multiple possible events for each individual. Women had fewer first ASCVD events than men, with only 310 composite ASCVD cases (2.9%) compared with 5175 (7.6%), respectively. Crude incidence rate of composite ASCVD events was greatest among HARE-defined White participants (187.5; 95% CI, 181.7-193.5 events per 10 000 person-years [PY]), slightly lower for Black participants (168.1; 95% CI, 158.8-177.8 events per 10 000 PY), and much lower for Hispanic participants (124.7; 95% CI, 111.5-139.1 events per 10 000 PY) (Table 1).

Crude cumulative incidence curves for composite ASCVD events are presented in **Figure 1** and for each ASCVD outcome in eFigure 1 in Supplement 1, stratified by percentile of composite PRS and traditional risk score. Both scores generally described a gradient of risk within the component and composite outcomes. The magnitude of this gradient from the lowest to highest percentiles was greater for the traditional risk score than the PRS. The trend in cumulative incidence of composite ASCVD events across PRS was largely driven by the CAD PRS.

Adjusted (for age, sex, and principal components of genetic ancestry) hazard ratios (HRs) for more extreme risk groups up to the top 0.5 percentile of PRS and traditional risk score are presented in **Table 2** and down to the bottom 0.5 percentile in eTable 4 in Supplement 1, compared with the middle decile of risk (45%-55%). The HRs differed by HARE group: a 1-SD increase of composite PRS increased the hazard for composite ASCVD events by 11% (95% CI, 5%-17%) in Black veterans, 12% (95% CI, 0-25%) in Hispanic veterans, and 20% (95% CI, 16%-24%) in White veterans. The per-SD HRs for traditional ASCVD risk scores were an order of magnitude greater than PRS in Black participants (HR, 1.96; 95% CI, 1.84-2.09), Hispanic participants (HR, 2.29; 95% CI, 2.02-2.59), and White participants (HR, 1.93; 95% CI, 1.86-2.00). In analyses of PRS categories, among White participants, the risk for composite ASCVD was positively associated with higher PRS groups, ranging from an HR of 1.42 (95% CI, 1.26-1.61) in the top 20% (compared with the middle decile) to an HR of 2.21 (95% CI, 1.55-3.15) in the top 0.5% of PRS, which was comparable with the top 0.5% of traditional risk score (HR, 2.62; 95% CI, 1.95-3.52).

Among component outcomes of ASCVD events, CAD PRS was associated with incident MI in non-Hispanic Black (HR, 1.10; 95% CI, 1.02-1.19), Hispanic (HR, 1.26; 95% CI, 1.09-1.46), and non-Hispanic White (HR, 1.23; 95% CI, 1.18-1.29) participants. Stroke PRS was associated with incident stroke in non-Hispanic White participants (HR, 1.15; 95% CI, 1.08-1.21). The combined CAD plus stroke PRS was associated with ASCVD deaths among non-Hispanic Black (HR, 1.19; 95% CI, 1.03-1.17) and non-Hispanic White (HR, 1.11; 95% CI, 1.03-1.21) participants.

The Harrell C indices for each incident ASCVD outcome are presented in **Figure 2** for the traditional risk model, combined traditional and polygenic risk model, and improvement of combined model over traditional risk model. The C statistics for traditional risk score (E model) and G × E models ranged from 0.64 to 0.68 for ASCVD outcomes (composite ASCVD events, MI, and stroke) and 0.70 to 0.71 for ASCVD death among HARE-defined non-Hispanic Black and White participants. Concordance of the traditional and G × E model was greater for Hispanic veterans, ranging from 0.70 to 0.73 for all outcomes except ASCVD death (C index, 0.78; 95% CI, 0.75-0.80). The addition of PRS to the traditional model (G × E vs E) increased the C index for all ASCVD outcomes by roughly 0.01 among Hispanic and White participants, but the incremental effects were smaller (C index, 0.004; 95% CI, 0-0.011) for ischemic stroke and for all nondeath outcomes among Black participants (composite CVD: C index, 0.004; 95% CI, 0.002-0.006; MI: C index, 0.006; 95% CI, 0.002-0.010).

Adding PRS to the traditional ASCVD risk model significantly improved reclassification of women around the intermediate risk threshold (5-year risk >3.5%) by 6.8% (95% CI,

Table 2. Incident Cardiovascular Disease (CVD) Hazard Ratios for High Traditional and Polygenic Risk Scores (PRSs)

	Hazard ratio (95% CI)					
	Non-Hispanic Black		Hispanic		Non-Hispanic White	
High PRS definition	PRS	Traditional risk score	PRS	Traditional risk score	PRS	Traditional risk score
Composite CVD (CAD PRS + AIS PRS)						
Continuous per SD increment	1.11 (1.05-1.17)	1.96 (1.84-2.09)	1.12 (1.00-1.25)	2.29 (2.02-2.59)	1.20 (1.16-1.24)	1.93 (1.86-2.00)
Top 20%[a]	1.18 (0.95-1.46)	1.94 (1.60-2.36)	0.79 (0.54-1.16)	3.07 (2.03-4.67)	1.42 (1.26-1.61)	1.76 (1.58-1.96)
Top 10%	1.29 (1.02-1.64)	2.01 (1.62-2.50)	0.83 (0.53-1.32)	3.24 (2.07-5.07)	1.56 (1.36-1.79)	2.08 (1.85-2.34)
Top 5%	1.20 (0.90-1.61)	2.30 (1.81-2.93)	NA	3.93 (2.40-6.41)	1.53 (1.30-1.81)	2.40 (2.10-2.74)
Top 1%	NA[b]	3.07 (2.10-4.48)	NA	NA	2.13 (1.63-2.79)	2.69 (2.17-3.34)
Top 0.5%	NA	NA	NA	NA	2.21 (1.55-3.15)	2.62 (1.95-3.52)
Myocardial infarction (CAD PRS)						
Continuous per SD increment	1.10 (1.02-1.19)	2.01 (1.83-2.20)	1.26 (1.09-1.46)	2.46 (2.07-2.92)	1.23 (1.18-1.29)	1.97 (1.87-2.06)
Top 20%	1.25 (0.93-1.68)	2.17 (1.64-2.87)	0.71 (0.45-1.13)	3.60 (1.96-6.59)	1.36 (1.16-1.58)	2.05 (1.77-2.37)
Top 10%	1.35 (0.97-1.88)	2.32 (1.71-3.15)	NA	4.09 (2.17-7.74)	1.50 (1.26-1.78)	2.32 (1.98-2.71)
Top 5%	1.40 (0.95-2.05)	2.82 (2.02-3.95)	NA	5.47 (2.80-10.69)	1.61 (1.31-1.96)	2.63 (2.20-3.13)
Top 1%	NA	4.06 (2.49-6.62)	NA	NA	2.23 (1.61-3.08)	3.61 (2.77-4.70)
Top 0.5%	NA	NA	NA	NA	2.19 (1.40-3.43)	3.09 (2.12-4.49)
Ischemic stroke (AIS PRS)						
Continuous per SD increment	1.05 (0.95-1.17)	1.90 (1.73-2.08)	1.08 (0.85-1.36)	2.09 (1.73-2.52)	1.15 (1.08-1.21)	1.79 (1.68-1.90)
Top 20%	0.85 (0.60-1.19)	2.48 (1.76-3.51)	1.71 (0.74-3.94)	2.14 (1.19-3.84)	1.22 (0.99-1.50)	1.64 (1.36-1.98)
Top 10%	0.94 (0.63-1.41)	2.77 (1.92-4.01)	NA	2.55 (1.36-4.78)	1.21 (0.95-1.53)	2.01 (1.64-2.46)
Top 5%	1.29 (0.82-2.04)	2.90 (1.92-4.38)	NA	NA	1.16 (0.86-1.56)	2.43 (1.95-3.04)
Top 1%	NA	NA	NA	NA	1.82 (1.14-2.90)	3.06 (2.16-4.35)
Top 0.5%	NA	NA	NA	NA	NA	NA
ASCVD death (CAD PRS + AIS PRS)						
Continuous per SD increment	1.19 (1.03-1.37)	2.61 (2.20-3.10)	1.24 (0.94-1.65)	3.84 (2.72-5.41)	1.11 (1.03-1.21)	2.60 (2.34-2.88)
Top 20%	1.30 (0.77-2.19)	2.89 (1.69-4.93)	NA	8.06 (1.93-33.68)	1.32 (0.97-1.81)	2.39 (1.81-3.15)
Top 10%	1.36 (0.76-2.45)	3.42 (1.95-6.01)	NA	NA	1.60 (1.13-2.27)	3.42 (2.58-4.55)
Top 5%	NA	4.54 (2.50-8.22)	NA	NA	1.49 (0.97-2.28)	3.92 (2.88-5.33)
Top 1%	NA	NA	NA	NA	NA	5.41 (3.52-8.33)
Top 0.5%	NA	NA	NA	NA	NA	NA

Abbreviations: AIS, acute ischemic stroke; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; NA, not applicable.

[a] Reference group equals middle 10% (45th to 55th percentiles) of risk score.

[b] NA, less than 10 events in risk group.

3.0%-10.6%) across all HARE groups combined (eTable 8 in Supplement 1), with the most reclassification occurring among Hispanic women at 19.0% (95% CI, 2.1%-39.9%), followed by Black women at 10.6% (95% CI, 3.1%-18.4%), and lowest among White women at 3.4% (95% CI, −0.1% to 7.4%) (**Figure 3**A). NRI of men was modest for the intermediate risk group for composite CVD (5-year risk >3.75%, 0.38%; 95% CI, 0.07%-0.68%) and significant around the high-risk threshold (5-year risk >10%) at 1.9% (95% CI, 1.0%-2.8%) overall, 1.9% (95% CI, 1.0%-3.0%) among White veterans (Figure 3B), and 3.2% (95% CI, −0.1% to 6.4%) among Hispanic veterans. Across both risk thresholds, NRI was approximately 1.4% higher in middle-aged adults aged 40 to 55 years (1.61%; 95% CI, −0.07% to 3.30%) compared with participants older than 55 years (0.25%; 95% CI, 0.03%-0.47%), with a net 3.2% (95% CI, 1.4%-5.0%) of middle-aged reclassified above or below high risk compared with the 1.8% (95% CI, 1.4%-5.0%) among participants older than 55 years. NRI was not present among Black participants except around the intermediate risk threshold for women. Hispanic participants had higher reclassification rates compared with White participants across all subgroups except for the intermediate risk group of middle-aged adults.

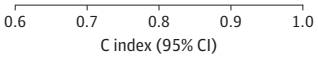
Although there were no reclassifications of the youngest statin-naive participants younger than 40 years (eFigure 2 in Supplement 1), a cohort including statin users exhibited a decreasing trend in reclassification with age: greatest among young participants, reduced in middle-aged adults, and lowest for older adults (eFigure 3 in Supplement 1). The median age of first ASCVD event was also 10 years lower in the top decile of PRS compared with traditional risk score (eFigure 4 in Supplement 1).

Continuous NRI (eFigure 5 in Supplement 1) was weak (<0.2) for HARE-defined Black and White participants and moderate for Hispanic participants (0.2 to 0.4) across all ASCVD

Figure 2. Harrell C Index for Traditional (Model E) and Combined Gene-Environment (Model G × E) Risk Models

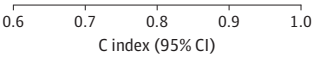
A Traditional risk model

Subgroup	C index (95% CI)
Composite CVD	
Black	0.67 (0.67 to 0.67)
Hispanic	0.71 (0.70 to 0.71)
White	0.66 (0.66 to 0.66)
Myocardial infarction	
Black	0.66 (0.66 to 0.67)
Hispanic	0.71 (0.70 to 0.72)
White	0.67 (0.67 to 0.67)
Ischemic stroke	
Black	0.67 (0.67 to 0.68)
Hispanic	0.70 (0.67 to 0.71)
White	0.64 (0.64 to 0.64)
ASCVD death	
Black	0.72 (0.71 to 0.73)
Hispanic	0.78 (0.75 to 0.80)
White	0.71 (0.70 to 0.71)



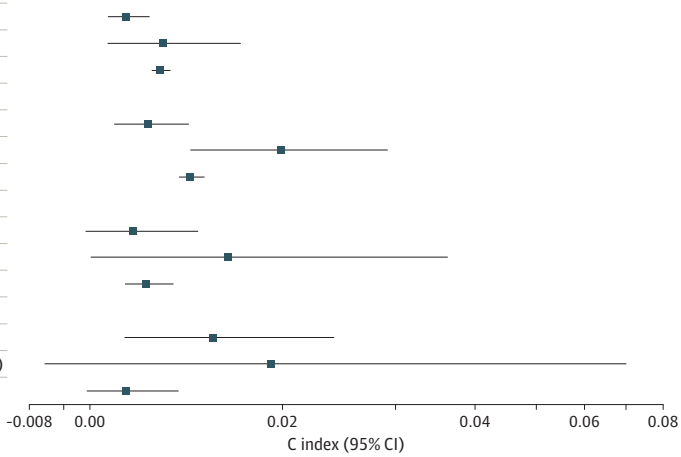
B Combined traditional and polygenic risk factor model

Subgroup	C index (95% CI)
Composite CVD	
Black	0.67 (0.67 to 0.67)
Hispanic	0.72 (0.71 to 0.72)
White	0.67 (0.67 to 0.67)
Myocardial infarction	
Black	0.67 (0.67 to 0.67)
Hispanic	0.73 (0.73 to 0.74)
White	0.68 (0.68 to 0.68)
Ischemic stroke	
Black	0.68 (0.68 to 0.68)
Hispanic	0.71 (0.70 to 0.71)
White	0.65 (0.65 to 0.65)
ASCVD death	
Black	0.73 (0.73 to 0.73)
Hispanic	0.80 (0.79 to 0.81)
White	0.71 (0.71 to 0.71)



C Change in C index (95% CI) after addition of polygenic scores to the traditional risk

Subgroup	C index (95% CI)
Composite CVD	
Black	0.004 (0.002 to 0.006)
Hispanic	0.008 (0.002 to 0.016)
White	0.007 (0.006 to 0.008)
Myocardial infarction	
Black	0.006 (0.002 to 0.010)
Hispanic	0.020 (0.010 to 0.031)
White	0.010 (0.009 to 0.012)
Ischemic stroke	
Black	0.004 (0 to 0.011)
Hispanic	0.014 (0 to 0.037)
White	0.006 (0.004 to 0.009)
ASCVD death	
Black	0.013 (0.004 to 0.025)
Hispanic	0.019 (-0.005 to 0.056)
White	0.004 (0 to 0.009)



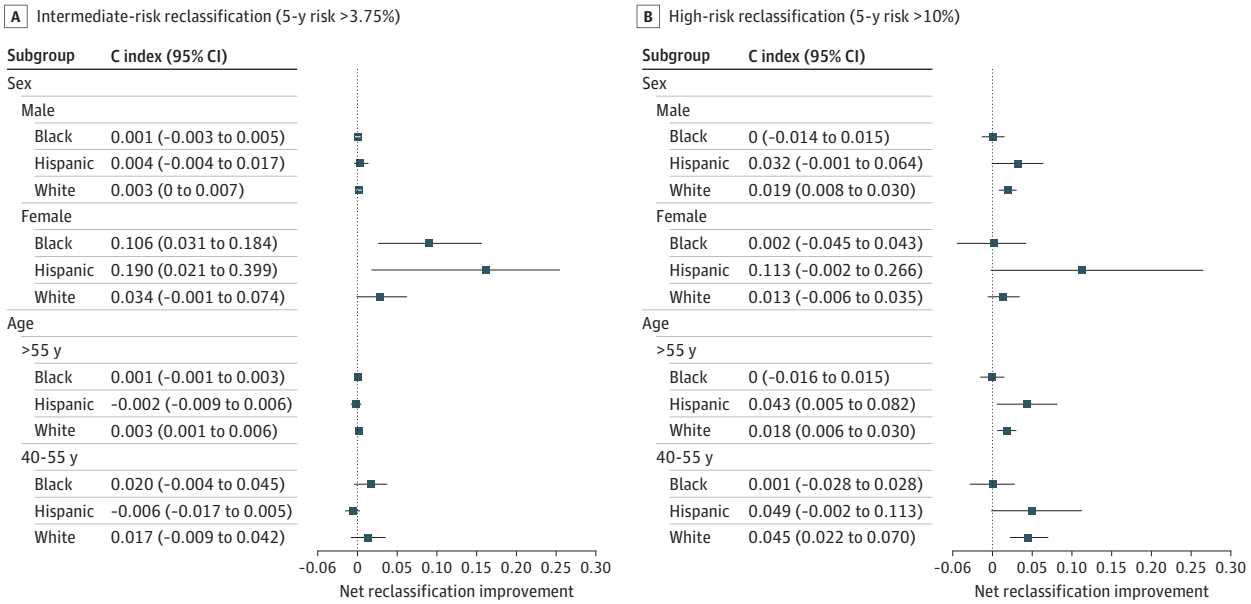
Harrell C index of the ancestry-specific risk models for each atherosclerotic cardiovascular disease (ASCVD) outcome is presented. The line segments represent 95% CIs constructed from 1000 bootstrap samples. A, Traditional risk model. B, Combined traditional and polygenic risk factor (G × E) model including an interaction between traditional and polygenic risk scores. C, Improvement in C index from the addition of polygenic scores to the traditional risk. C index ranges from 0.5 (which indicates a risk score is no better than a coin flip at predicting which patient [in each pair of patients] will have an event first) to 1, which indicates a risk score perfectly predicts which patient (of each pair) has an event first. Change in C index is calculated by subtracting the traditional model's C index from the G × E model's C index, with positive values indicating an improvement from incorporation of polygenic scores. CVD indicates cardiovascular disease.

outcomes, except ASCVD death. Compared with the traditional risk model, the combined traditional and PRS model predicted a greater ASCVD risk among events (and reduced risk for nonevents) for a net 12.2% (95% CI, 5.8%-18.4%) of Black participants, 26.0% (95% CI, 13.6%-37.1%) of Hispanic participants, and 13.8% (95% CI, 10.0%-17.4%) of White participants. Continuous NRI increased when including statin users and was moderate across all HARE groups at 14.4% (95% CI, 8.1%-20.5%) among Black participants, 25.7% (95% CI, 14.7%-36.3%) among Hispanic participants, and 20.1% (95% CI, 16.7%-23.7%) among White participants. Reclassification tables for other ASCVD outcomes are presented in eTables 5 to 7 in Supplement 1.

Discussion

In this large multiancestry prognostic cohort study, PRSs derived from both CAD and ischemic stroke GWAS summary statistics were associated with incident ASCVD events in a primary prevention population. Among the 3 populations examined, PRSs were statistically significantly associated with

Figure 3. Net Reclassification Improvement for Composite Cardiovascular Disease (CVD) From Inclusion of Polygenic Risk Scores



A and B present net intermediate and high-risk reclassification improvement, respectively, from the addition of polygenic scores to the traditional risk model for composite CVD, stratified by ancestry, age group, and sex.

incident MI, ischemic stroke, ASCVD death, and composite ASCVD events with a higher (but still modest) degree of improved reclassification observed for women compared with men and for younger-onset disease compared with older-onset disease.

Previous studies of incident ASCVD in predominantly European-ancestry populations have reported small but consistent improvements in model performance when adding PRS.[34] These studies have demonstrated changes in C statistics between 0.009 to 0.02 and 10-year NRI between 2.7% to 4.7%. Fewer studies have evaluated PRS in non-European cohorts and have generally observed attenuated magnitudes of association and reclassification.[4,5,12] The present study included 18 505 Black and 6785 Hispanic participants, representing an important contribution to polygenic ASCVD risk stratification research, where to date the largest study has included only 55 ASCVD events among 823 Hispanic participants.[4] Similar to prior reports, European-derived PRS was significantly associated with incident ASCVD events in Black and Hispanic MVP participants but with reduced or no improvement in net reclassification. Continued advances in multiancestry GWAS and PRS development are expected to further improve PRS performance in populations of diverse genetic ancestry.[35] Whether to include the sociocultural constructs of race and ethnicity in clinical prediction models is controversial but remains the standard of care in ASCVD risk estimation and prevention.[36,37] Further research is needed before consensus can be reached about the role of socially defined race and ethnicity and genetically defined ancestry in risk prediction, with or without PRS.[38,39]

Although most other studies have evaluated a CAD PRS for ASCVD risk stratification, this study examined the utility of published PRSs for 2 components of ASCVD (CAD and ischemic stroke) across 4 ASCVD outcomes (MI, ischemic stroke, ASCVD death, and composite ASCVD events). Physicians use models that estimate 10-year risk of ASCVD events, and thus, the inclusion of both CAD- and stroke-associated PRS may be more appropriate to evaluate the potential for PRSs to improve existing clinical models. Across HARE groups, this study observed that the CAD PRS was associated with incident MI, the stroke PRS was associated with incident ischemic stroke, and the combination of the 2 PRSs was associated with ASCVD death and composite ASCVD events. In all models, the risk scores constructed from traditional risk factors conferred greater ASCVD risk per SD compared with PRS. Further research is needed to determine the best approach to combining PRS for clinical risk stratification of multiple phenotypes, perhaps leveraging transcriptomic data or more advanced computational approaches to PRS construction.[4,30,40] Improved understanding of the genetic architecture of CVD may inform a paradigm change in clinical practice, favoring the identification and risk management of more precise disease phenotypes and corresponding prevention strategies. Either way, for a clinical prediction model to be widely implemented, it requires inputs that are already clinically available or readily attainable, and several challenges impede the implementation of increasingly complex prediction models at the point of patient care.

Despite few cases and low statistical power among younger strata, the higher NRI observed among younger participants in the MVP is largely concordant with independent studies of Europeans aged 40 to 55 years (NRI = 10.3%)[4] and younger than 50 years (13.5% reclassified to intermediate risk) in the UK[41] and Black participants in the US (8.5%). A Finnish study simi-

larly observed that 12.6% of the coronary events that occurred before 55 years of age were attributable to high PRS risk compared with 2.5% for later-onset events.[42] The older VHA patient population and analysis of first ASCVD events after MVP enrollment likely excluded other early-life events where genetic factors may contribute more to ASCVD development. Still, to our knowledge, this was the first multiancestry study to evaluate PRS for predicting first ASCVD events in individuals younger than 40 years.[43,44]

Limitations

There are a few study limitations to note. First, the PRSs used were developed in predominantly European ancestry populations and were not multiancestry or transancestry scores. Second, due to limited follow-up in the MVP, only 5-year ASCVD risk was estimated instead of the usual 10-year risk. Third, the high rate of statin use at baseline and the large number of participants with clinical CAD who may have undergone revascularization procedures without experiencing a qualifying outcome during the short follow-up period may have reduced the discriminative potential of a PRS for CAD across all ages. Supporting this possibility is a growing body of evidence demonstrating that participants in the highest tertile of a PRS derive the greatest benefit from a statin, with a near halving of risk in both primary and secondary prevention settings, whereas those in the bottom tertile derive little to no benefit over the same period of follow-up.[45-47] Lastly, demographic composition was predominantly male. Although the sample included almost 11 000 women, sex-specific differences in event rates may make the results less generalizable to women.

Whether the improved discrimination observed in this study (and others) supports the integration of PRSs in clinical practice cannot be answered definitively without clinical trials.[48,49] Arguments against clinical utility of PRSs have historically been rooted in the low absolute magnitude of incremental discrimination such as the delta C statistic—a low-power procedure—or the NRI.[48,50] However, there remains considerable debate on which metrics should be used to demonstrate clinical validity. Net benefit, for example, may be most appropriate when the harm of overtreatment is minimal, such as lifestyle counseling.[31,51-56] The 2019 American College of Cardiology/American Heart Association cholesterol guideline emphasizes shared decision-making between physician and patients at moderate or high 10-year risk (ie, >5.0%), including consideration of risk-enhancing factors beyond traditional ASCVD risk models.[57] Under these circumstances, a specific threshold of risk does not exist and even small improvements in discrimination may be clinically helpful when applied to large populations at risk. The recent American Heart Association scientific statement on PRSs further clarifies these potential benefits for CAD risk stratification.[11] It may be reasonable to consider a PRS as an additional risk-enhancing factor based on the performance of the most recently constructed genome-wide PRS. This may be better supported if anticipated improvements in PRSs are actualized over time.[49]

Conclusions

In conclusion, results of this prognostic study suggest that PRSs for CAD and ischemic stroke derived from largely European ancestry populations were statistically significantly associated with first ASCVD events in the multiancestry MVP cohort, but reclassification improvement was modest. This study also reinforces the need for multiancestry PRSs to improve risk stratification of non-European populations. The results suggest the possibility that the predictive utility of PRS may be relatively higher for women and younger populations, but more studies, especially clinical trials, are needed before definitive conclusions can be made in this regard.

ARTICLE INFORMATION

Accepted for Publication: March 9, 2023.

Published Online: May 3, 2023. doi:10.1001/jamacardio.2023.0857

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Statistical analysis: Vassy, Posner, Gagnon, Madduri, McMahon, Casas, Sun.
Obtained funding: Galloway, Madduri, Tsao, Assimes, Gaziano, Cho, Wilson.
Administrative, technical, or material support: Vassy, Ho, Galloway, Tanukonda, Houghton, Madduri, Tsao, Gaziano, Cho, Wilson.
Supervision: Vassy, Madduri, Assimes, Gaziano, Sun, Cho, Wilson.

Conflict of Interest Disclosures: Dr Vassy reported receiving grants from the Veterans Health Administration and the National Institutes of Health and personal fees from Nalagenetics outside the submitted work. Dr Tsao reported receiving grants from the VA Office of Research and Development during the conduct of the study. Dr Damrauer reported receiving grants from Renalytix AI and the US Department of Veterans Affairs outside the submitted work and having a patent for genetic risk prediction for venous thromboembolic disease pending application filed by the US Department of

Veterans Affairs in accordance with Federal regulatory requirements. Dr O'Donnell reported being an employee of Novartis Institute for Biomedical Research during the conduct of the study. Dr Casas reported being an employee at Novartis Institute for Biomedical Research toward the completion of this study. Dr Sun reported receiving grants from the National Institutes of Health outside the submitted work. Dr Wilson reported receiving grants from the Veterans Administration during the conduct of the study. No other disclosures were reported.

Funding/Support: This project is supported by VA Merit Grant BX004821 (Drs Wilson and Cho); grants I01-BX004821 (Drs Cho and Tsao), I01-BX003340 (Drs Wilson and Cho), grant VA HSR RES 13-457 from the VA Informatics and Computing Infrastructure; and support for VA/CMS data from the Department of Veterans Affairs, VA Health Services Research and Development Service, VA Information Resource Center (projects SDR 02-237 and 98-004).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

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Supplementary Online Content

Vassy JL, Posner DC, Ho YL, et al. Cardiovascular disease risk assessment using traditional risk factors and polygenic risk scores in the million veteran program. *JAMA Cardiol*. Published online May 3, 2023. doi:10.1001/jamacardio.2023.0857

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Genetically Informed Ancestry (GIA) and HARE Classification in the Million Veteran Program (MVP)

		Genetically Informed Ancestry (GIA)					HARE total (not NA)
		AFR	EAS	EUR	AMR	NA	
Harmonized Ancestry and Race/Ethnicity (HARE)	Non-Hispanic Black	**122,114**	0	0	181	*825*	**122,295**
	Asian	2	**6,684**	32	25	*1,586*	**6,743**
	Non-Hispanic White	3	1	**456,030**	5,650	*3,277*	**461,684**
	Hispanic	190	28	485	**51,195**	*285*	**51,898**
	NA	*1,019*	*363*	*1,173*	*4,060*	*3,374*	
GIA Total (not NA)		**122,309**	**6,713**	**456,547**	**57,051**		

* GIA super populations: AFR = African, EAS = East Asian, EUR = European, AMR = Ad Mixed American

eTable 1 caption: Agreement between HARE and GIA classifications were very high (>99%) for all ancestries except the AMR (Ad Mixed American) super population. 5,650 participants from the AMR-ancestry were classified as non-Hispanic White by the HARE algorithm, and a further 4,060 were excluded due to disagreement between self-identified race/ethnicity and GIA.

eTable 2. Electronic Health Record Codes (*ICD-9*, *ICD-10*, CPT/HCPCS) for ASCVD Outcomes

Outcome	ICD-9 Codes	ICD-10 Codes	CPT/HCPCS Codes
Composite ASCVD	Myocardial Infarction, Ischemic Stroke, or ASCVD Death Codes		
Composite ASCVD and Revascularization	Composite ASCVD, Percutaneous Coronary Intervention, and Coronary Artery Bypass Graft		
Myocardial Infarction	410, 411.0, I21, I22	410, 411.0, I21, I22	
Ischemic Stroke	433.x1, 434 (excluding 434.x0), 436, 437.0, 437.6	I63.xx9, I63.20, I63.22, I63.30, I63.40, I63.50, I63.59, I67.2, I67.6, I67.89	
ASCVD Death		I10, I11, I13, I16, I20-I25, I46, I63, I67, I70, I74, I75, G45	
Percutaneous Coronary Intervention			C9602-C9608, 92920-92921, 92924-92925, 92933-92934, 92937, 92995, 92966, 93540, 93564, 93570, 92928, 92929
Coronary Artery Bypass Graft			C9600-C9608, G8574, 33510-33523, 33533-33536, 33572, excluding 3351F, 3352F, 3353F, 33515

eTable 3. Baseline Characteristics and ASCVD Events Stratified by Sex

	Number (%)		
Baseline Characteristic	**Total cohort (N = 79,151)**	**Male (n = 68,503)**	**Female (n = 10,648)**
Follow-up, years, median (5th-95th percentile)	4.3 (0.7-6.9)	4.3 (0.7-6.9)	4.0 (0.5-6.8)
Age, mean (SD), y	57.8 (13.7)	59.3 (13.3)	48.6 (12.6)
Cardiovascular Risk Factors			
Total cholesterol, mean (SD), mg/dL	157.8 (40.6)	157.3 (40.3)	161.4 (42.3)
HDL-C, mean (SD), mg/dL	49.8 (17)	48.6 (16.6)	57.4 (17.4)
LDL-C, mean (SD), mg/dL	109.4 (33.3)	108.6 (33.2)	114.4 (34.1)
Systolic blood pressure, mean (SD), mm Hg	131.3 (13.4)	132.1 (13.2)	125.7 (13.1)
Current smoker	8,435 (10.7)	7,530 (11)	905 (8.5)
Former smoker	47,670 (60.2)	42,705 (62.3)	4,965 (46.6)
Never smoker	23,046 (29.1)	18,268 (26.7)	4,778 (44.9)
Diabetes	17,177 (21.7)	15,643 (22.8)	1,534 (14.4)
Medications			
Blood pressure treatment	36,673 (46.3)	33,365 (48.7)	3,308 (31.1)
No. of events (2011 - 2018)			
Composite ASCVD (%)	5,485 (6.9)	5,175 (7.6)	310 (2.9)
Composite ASCVD and revascularization (%)	6,628 (8.4)	6,265 (9.1)	363 (3.4)
ASCVD Death (%)	867 (1.1)	836 (1.2)	31 (0.3)
Acute ischemic stroke (%)	1,933 (2.4)	1,781 (2.6)	152 (1.4)
Myocardial Infarction (%)	3,186 (4)	3,036 (4.4)	150 (1.4)
Crude Incidence rate / 10k Person Years (2011 - 2018)			
Composite ASCVD (95% CI)	177.7 (173.0-182.5)	193.0 (187.8-198.3)	76.4 (68.2-85.4)
Composite ASCVD and revascularization (95% CI)	216.6 (211.4-221.9)	235.9 (230.1-241.8)	89.7 (80.7-99.5)
ASCVD Death (95% CI)	27.0 (25.2-28.8)	29.9 (27.9-32.0)	7.5 (5.1-10.6)
Acute ischemic stroke (95% CI)	61.0 (58.3-63.8)	64.5 (61.5-67.6)	37.2 (31.5-43.6)
Myocardial Infarction (95% CI)	100.9 (97.4-104.4)	110.5 (106.6-114.5)	36.5 (30.9-42.9)

eTable 4. Hazard Ratios for MVP Incident ASCVD Events for Low Traditional and Polygenic Risk Scores

High PRS definition	Hazard Ratio (95% CI)					
	Non-Hispanic White		Non-Hispanic Black		Hispanic	
Composite ASCVD Events	Polygenic Risk Score	Traditional Risk Score	Polygenic Risk Score	Traditional Risk Score	Polygenic Risk Score	Traditional Risk Score
Continuous per SD reduction	0.80 (0.77, 0.82)	0.48 (0.46, 0.50)	0.86 (0.81, 0.91)	0.45 (0.42, 0.48)	0.79 (0.72, 0.88)	0.35 (0.32, 0.40)
Bottom 20%*	0.75 (0.67, 0.84)	0.16 (0.13, 0.20)	0.95 (0.76, 1.19)	0.17 (0.12, 0.25)	0.74 (0.50, 1.10)	N/A
Bottom 10%	0.66 (0.58, 0.76)	0.10 (0.07, 0.14)	0.90 (0.68, 1.18)	N/A	0.76 (0.47, 1.24)	N/A
Bottom 5%	0.64 (0.54, 0.76)	N/A	0.79 (0.55, 1.15)	N/A	N/A	N/A
Bottom 1%	0.61 (0.42, 0.86)	N/A	N/A	N/A	N/A	N/A
Bottom 0.5%	N/A**	N/A	N/A	N/A	N/A	N/A
Myocardial Infarction						
Continuous per SD reduction	0.75 (0.73, 0.78)	0.52 (0.50, 0.54)	0.88 (0.82, 0.94)	0.47 (0.44, 0.51)	0.77 (0.68, 0.87)	0.36 (0.31, 0.41)
Bottom 20%	0.70 (0.61, 0.81)	0.19 (0.15, 0.24)	0.89 (0.67, 1.17)	0.23 (0.15, 0.35)	0.40 (0.25, 0.66)	N/A
Bottom 10%	0.63 (0.53, 0.75)	N/A	0.88 (0.63, 1.23)	N/A	0.52 (0.30, 0.91)	N/A
Bottom 5%	0.60 (0.48, 0.75)	N/A	0.62 (0.39, 0.99)	N/A	N/A	N/A
Bottom 1%	N/A	N/A	N/A	N/A	N/A	N/A
Bottom 0.5%	N/A	N/A	N/A	N/A	N/A	N/A
Ischemic Stroke						
Continuous per SD reduction	0.89 (0.84, 0.94)	0.48 (0.45, 0.52)	0.87 (0.78, 0.96)	0.43 (0.39, 0.48)	0.85 (0.69, 1.04)	0.36 (0.29, 0.44)
Bottom 20%	0.91 (0.72, 1.14)	0.23 (0.16, 0.33)	0.92 (0.63, 1.35)	N/A	0.76 (0.35, 1.63)	N/A
Bottom 10%	0.95 (0.73, 1.24)	N/A	0.75 (0.45, 1.24)	N/A	N/A	N/A
Bottom 5%	0.83 (0.59, 1.16)	N/A	0.97 (0.51, 1.83)	N/A	N/A	N/A
Bottom 1%	N/A	N/A	N/A	N/A	N/A	N/A
Bottom 0.5%	N/A	N/A	N/A	N/A	N/A	N/A
ASCVD Death						
Continuous per SD reduction	0.82 (0.77, 0.88)	0.29 (0.26, 0.32)	0.89 (0.77, 1.03)	0.31 (0.26, 0.37)	0.85 (0.68, 1.07)	0.25 (0.19, 0.34)
Bottom 20%	0.82 (0.62, 1.08)	N/A	0.58 (0.34, 0.99)	N/A	N/A	N/A
Bottom 10%	0.67 (0.48, 0.94)	N/A	0.78 (0.42, 1.44)	N/A	N/A	N/A
Bottom 5%	0.64 (0.42, 0.97)	N/A	N/A	N/A	N/A	N/A
Bottom 1%	N/A	N/A	N/A	N/A	N/A	N/A
Bottom 0.5%	N/A	N/A	N/A	N/A	N/A	N/A

* Reference group = middle 10% (45th to 55th percentiles) of risk score
** N/A = <10 events in the selected risk group.

eTable 5. Reclassification of 5-Year Predicted Myocardial Infarction Including Both Statin-Naïve and Statin Users

Correctly Reclassified | Incorrectly Reclassified

A. All participants

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	786	186	972 (27.9)
	> 3.75%	146	2360	2506 (72.1)
	Total N (%)	932 (26.8)	2546 (73.2)	3478 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	18657	1714	20371 (50.6)
	> 3.75%	2451	17432	19883 (49.4)
	Total N (%)	21108 (52.4)	19146 (47.6)	40254 (100)

B. Non-Hispanic White

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	459	149	608 (23.9)
	> 3.75%	125	1811	1936 (76.1)
	Total N (%)	584 (23.0)	1960 (77.0)	2544 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	10645	1392	12037 (43.9)
	> 3.75%	2111	13248	15359 (56.1)
	Total N (%)	12756 (46.6)	14640 (53.4)	27396 (100)

C. Non-Hispanic Black

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	241	23	264 (38.8)
	> 3.75%	14	403	417 (61.2)
	Total N (%)	255 (37.4)	426 (62.6)	681 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	5668	224	5892 (64.0)
	> 3.75%	200	3120	3320 (36.0)
	Total N (%)	5868 (63.7)	3344 (36.3)	9212 (100)

D. Hispanic

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	86	14	100 (39.5)
	> 3.75%	7	146	153 (60.5)
	Total N (%)	93 (36.8)	160 (63.2)	253 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	2344	98	2442 (67.0)
	> 3.75%	140	1064	1204 (33.0)
	Total N (%)	2484 (68.1)	1162 (31.9)	3646 (100)

eTable 6. Reclassification of 5-Year Predicted Acute Ischemic Stroke Including Both Statin-Naïve and Statin Users

Correctly Reclassified | Incorrectly Reclassified

A. All participants

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	1276	49	1325 (83.0)
	> 3.75%	32	239	271 (17.0)
	Total N (%)	1308 (82.0)	288 (18.0)	1596 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	37290	534	37824 (93.3)
	> 3.75%	465	2249	2714 (6.7)
	Total N (%)	37755 (93.1)	2783 (6.9)	40538 (100)

B. Non-Hispanic White

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	871	32	903 (86.2)
	> 3.75%	21	124	145 (13.8)
	Total N (%)	892 (85.1)	156 (14.9)	1048 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	25853	354	26207 (94.7)
	> 3.75%	291	1186	1477 (5.3)
	Total N (%)	26144 (94.4)	1540 (5.6)	27684 (100)

C. Non-Hispanic Black

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	303	15	318 (73.1)
	> 3.75%	11	106	117 (26.9)
	Total N (%)	314 (72.2)	121 (27.8)	435 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	7922	164	8086 (87.9)
	> 3.75%	157	956	1113 (12.1)
	Total N (%)	8079 (87.8)	1120 (12.2)	9199 (100)

D. Hispanic

		Traditional x Polygenic Risk Score (GxE) Model		
	Traditional Model	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
Events	**≤ 3.75%**	102	2	104 (92.0)
	> 3.75%	0	9	9 (8.0)
	Total N (%)	102 (90.3)	11 (9.7)	113 (100)
Nonevents	**Traditional Model**	**≤ 3.75%**	**> 3.75%**	**Total N (%)**
	≤ 3.75%	3515	16	3531 (96.6)
	> 3.75%	17	107	124 (3.4)
	Total N (%)	3532 (96.6)	123 (3.4)	3655 (100)

eTable 7. Reclassification of 5-Year Predicted ASCVD Death Including Both Statin-Naïve and Statin Users

	Correctly Reclassified	Incorrectly Reclassified

A. All participants

	Traditional Model	Traditional x Polygenic Risk Score (GxE) Model		
		≤ 3.75%	> 3.75%	Total N (%)
Events	≤ 3.75%	716	21	737 (79.8)
	> 3.75%	15	172	187 (20.2)
	Total N (%)	731 (79.1)	193 (20.9)	924 (100)
Nonevents	≤ 3.75%	38832	256	39088 (95.5)
	> 3.75%	249	1602	1851 (4.5)
	Total N (%)	39081 (95.5)	1858 (4.5)	40939 (100)

B. Non-Hispanic White

	Traditional Model	Traditional x Polygenic Risk Score (GxE) Model		
		≤ 3.75%	> 3.75%	Total N (%)
Events	≤ 3.75%	508	19	527 (76.5)
	> 3.75%	13	149	162 (23.5)
	Total N (%)	521 (75.6)	168 (24.4)	689 (100)
Nonevents	≤ 3.75%	26142	231	26373 (94.4)
	> 3.75%	219	1332	1551 (5.6)
	Total N (%)	26361 (94.4)	1563 (5.6)	27924 (100)

C. Non-Hispanic Black

	Traditional Model	Traditional x Polygenic Risk Score (GxE) Model		
		≤ 3.75%	> 3.75%	Total N (%)
Events	≤ 3.75%	155	2	157 (90.2)
	> 3.75%	2	15	17 (9.8)
	Total N (%)	157 (90.2)	17 (9.8)	174 (100)
Nonevents	≤ 3.75%	9099	18	9117 (97.7)
	> 3.75%	23	194	217 (2.3)
	Total N (%)	9122 (97.7)	212 (2.3)	9334 (100)

D. Hispanic

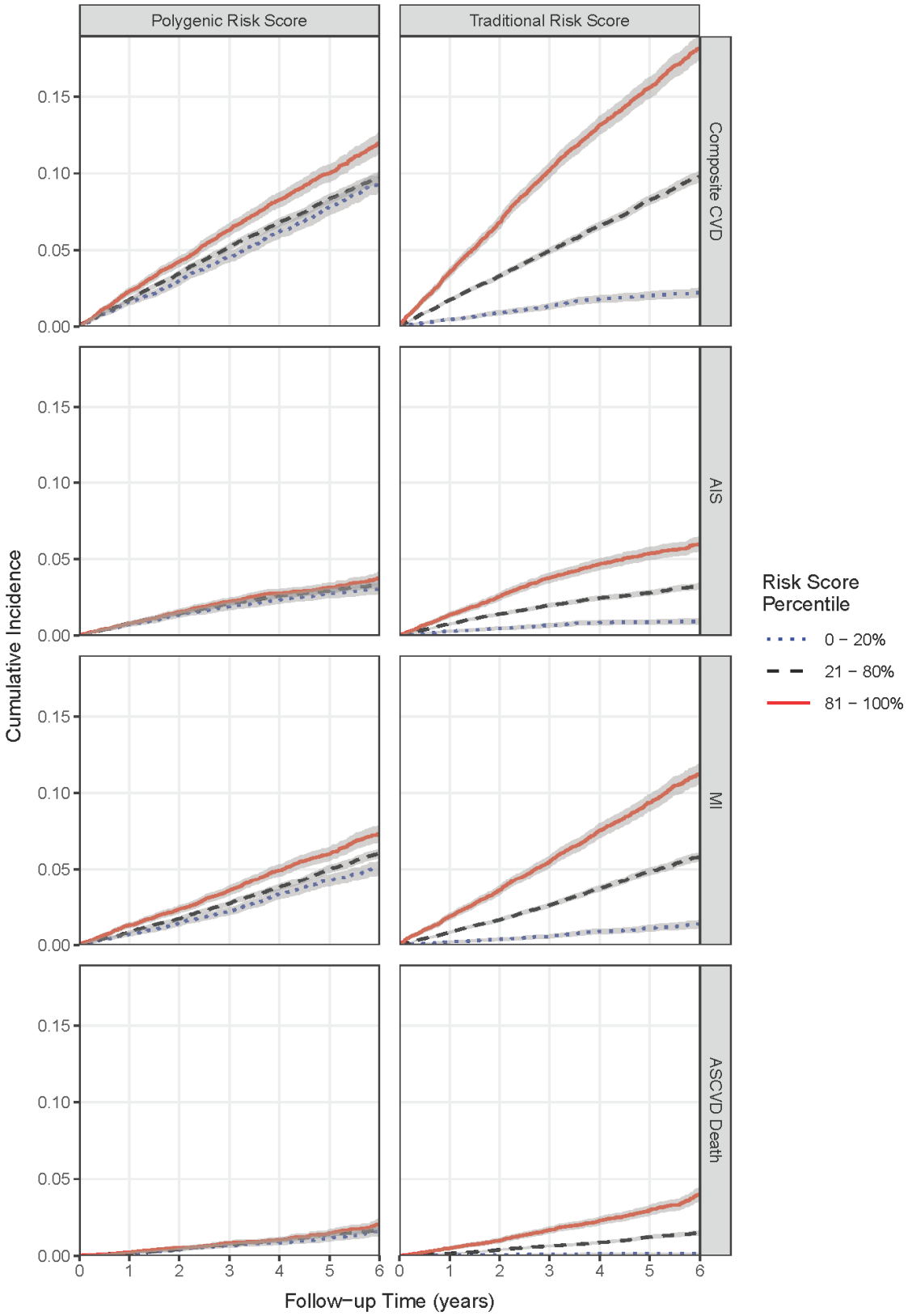
	Traditional Model	Traditional x Polygenic Risk Score (GxE) Model		
		≤ 3.75%	> 3.75%	Total N (%)
Events	≤ 3.75%	53	0	53 (86.9)
	> 3.75%	0	8	8 (13.1)
	Total N (%)	53 (86.9)	8 (13.1)	61 (100)
Nonevents	≤ 3.75%	3591	7	3598 (97.7)
	> 3.75%	7	76	83 (2.3)
	Total N (%)	3598 (97.7)	83 (2.3)	3681 (100)

eTable 8. Net Reclassification Improvement From Inclusion of Polygenic Scores Stratified by Age and Sex

5-year Risk Group	Subgroup	Net Reclassified		Total N		NRI+	NRI-	NRI [95% CI]
		Event	Non-Event	Event	Non-event			
Intermediate (3.75% - 10%)	Male	-4	110	4731	23856	-0.08%	0.46%	0.38% [0.07%, 0.68%]
	Female	20	-6	287	3450	6.97%	-0.17%	6.79% [3.01%, 10.58%]
	>55 yrs	-6	72	4151	18267	-0.14%	0.39%	0.25% [0.03%, 0.47%]
	40 to 55 yrs	-2	122	777	6526	-0.26%	1.87%	1.61% [-0.07%, 3.30%]
High (≥10%)	Male	62	140	4731	23856	1.31%	0.59%	1.90% [0.97%, 2.82%]
	Female	5	15	287	3450	1.74%	0.43%	2.18% [0.11%, 4.24%]
	>55 yrs	31	194	4151	18267	0.75%	1.06%	1.81% [0.81%, 2.81%]
	40 to 55 yrs	33	-69	777	6526	4.25%	-1.06%	3.19% [1.41%, 4.97%]

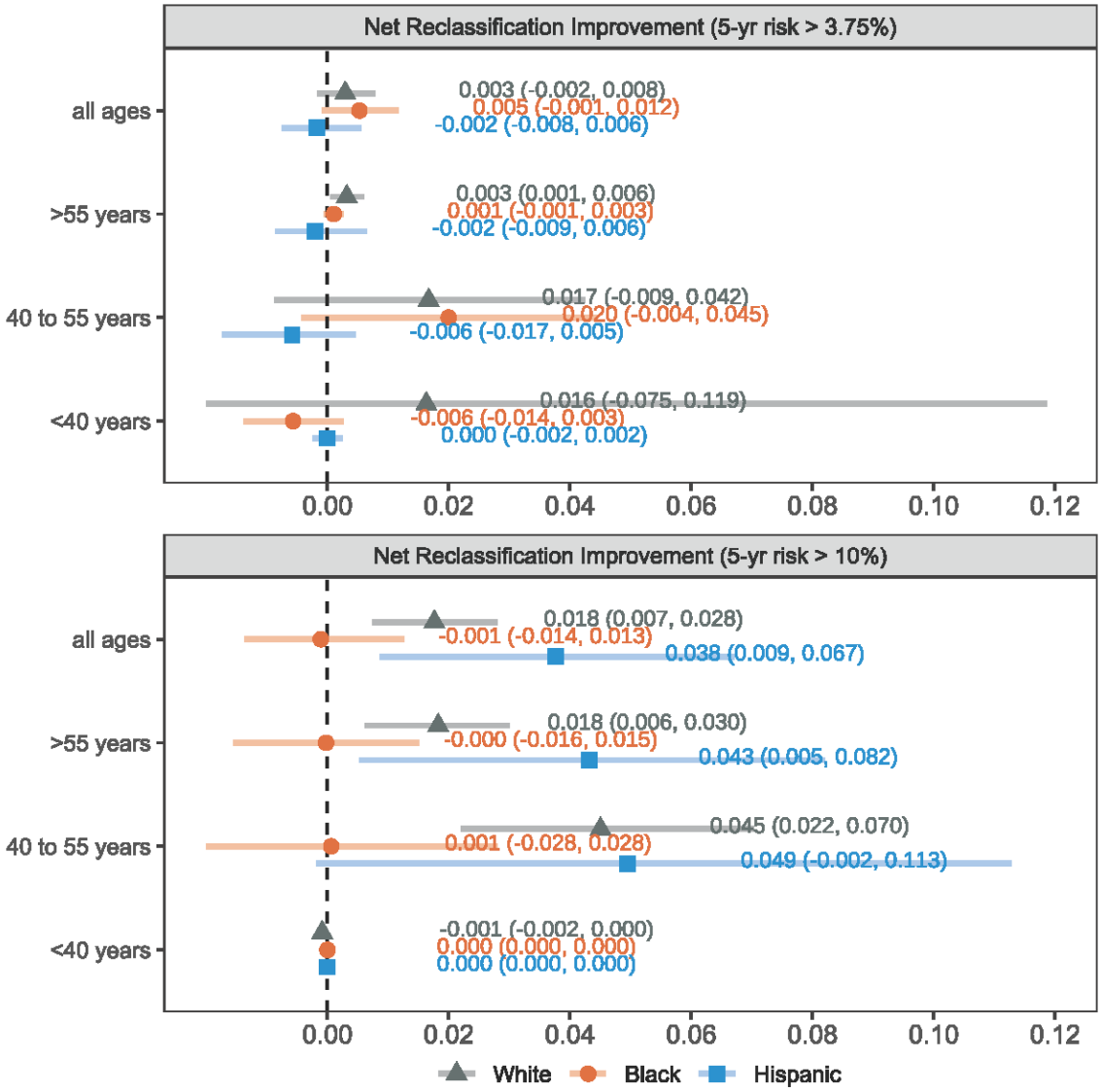
eTable 8 contains an abbreviated reclassification table for all ancestries combined. Net reclassified events are the number of events reclassified upwards (into the Intermediate or High risk groups) minus the number of events reclassified downwards. Net reclassified non-events are the number of non-events reclassified downwards minus the number of events reclassified upwards. The traditional model includes age, sex, and 5 principal components of genetic ancestry (to be comparable to the genetic model), and the 5-year risk cutoffs are half the clinically relevant 10-year risk thresholds from the ACC2019 guidelines. Among ASCVD events in the middle-aged subgroup (ages 40 to 55 years), the net proportion of correct reclassifications was NRI+ = 33/777= 4.25%, and among non-events was NRI- = -69/6526 = -1.06%. The overall net reclassification index is defined as the sum of the net reclassification proportions for events and nonevents (NRI = 4.25% + -1.06% = 3.19%).

eFigure 1. Cumulative Incidence of ASCVD Events



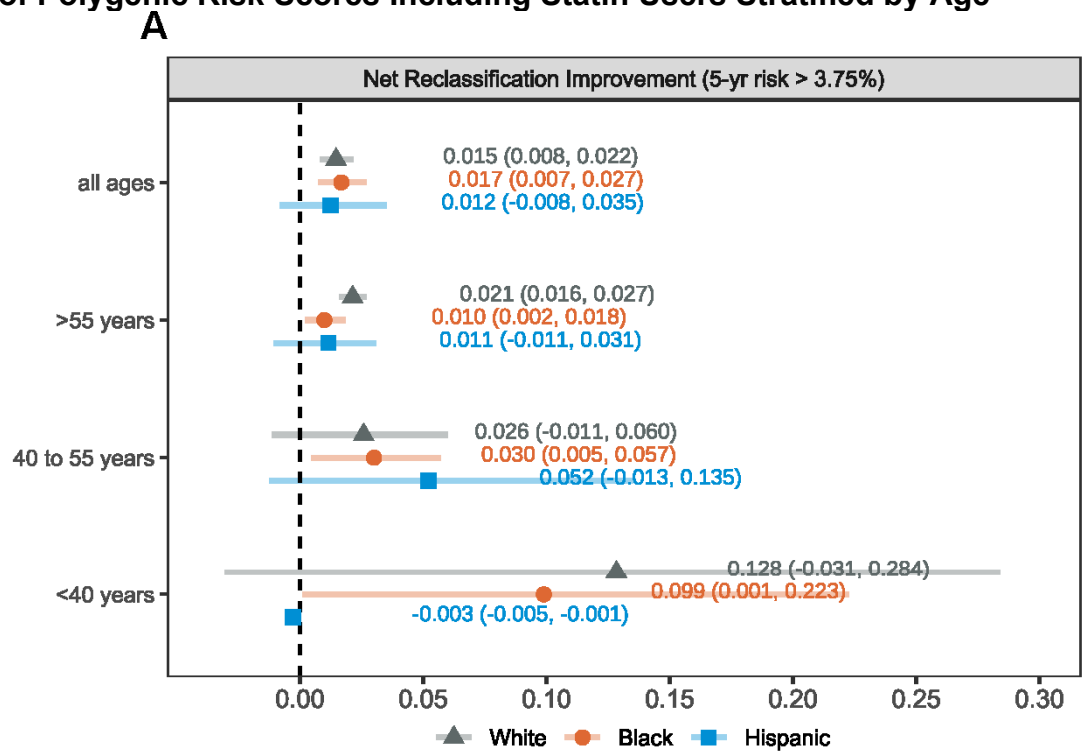
eFigure 1 caption: Cumulative incidence of Composite ASCVD, Acute Ischemic Stroke, Myocardial Infarction (MI), and ASCVD Death are plotted over 6 years of follow up according to percentile groups for Polygenic Risk Scores and Traditional Risk Scores.
Key: Risk score percentile 0-20% (dotted, blue), 21-80% (dashed, black), 81-100% (solid, red).

eFigure 2. Categorical Net Reclassification Index for Incident Composite ASCVD Among Statin-Naïve Participants Outcomes Stratified by Age Group



eFigure 2 caption:
Top Panel: Categorical Net Reclassification Improvement for intermediate risk (5-year risk >3.75%) among statin-naïve patients is shown for Composite ASCVD, Myocardial Infarction, Ischemic Stroke, and ASCVD Death.
Bottom Panel: Categorical Net Reclassification Improvement for high risk (5-year risk >10%) among statin-naïve patients is shown for Composite ASCVD, Myocardial Infarction, Ischemic Stroke, and ASCVD Death.
Key: Estimates and 95% confidence intervals are shown for White (black, triangle), Black (red, circle), and Hispanic (blue, square) population groups.

eFigure 3. Net Reclassification Index for Intermediate Risk (5-year risk > 3.75%) From Inclusion of Polygenic Risk Scores Including Statin Users Stratified by Age



		Correctly Reclassified	Incorrectly Reclassified

B All ages — NRI (95% CI) = 1.65% (1.11, 2.18%); NRI+ = 0.27%; NRI- = 1.38%

	Traditional	Traditional x PRS ≤ 3.75%	Traditional x PRS > 3.75%
Events	≤ 3.75%	404	103
	> 3.75%	88	5024
Non-events	≤ 3.75%	10663	803
	> 3.75%	1342	26276

C >55 yrs — NRI (95% CI) = 1.96% (1.48, 2.44%); NRI+ = -0.50%; NRI- = 2.46%

	Traditional	Traditional x PRS ≤ 3.75%	Traditional x PRS > 3.75%
Events	≤ 3.75%	91	33
	> 3.75%	56	4400
Non-events	≤ 3.75%	1163	246
	> 3.75%	854	22407

D 40-55 yrs — NRI (95% CI) = 2.94% (0.88, 5.00%); NRI+ = 3.10%; NRI- = -0.15%

	Traditional	Traditional x PRS ≤ 3.75%	Traditional x PRS > 3.75%
Events	≤ 3.75%	238	59
	> 3.75%	30	610
Non-events	≤ 3.75%	5066	473
	> 3.75%	458	3721

E <40 yrs — NRI (95% CI) = 7.67% (0.95, 14.40%); NRI+ = 8.82%; NRI- = -1.15%

	Traditional	Traditional x PRS ≤ 3.75%	Traditional x PRS > 3.75%
Events	≤ 3.75%	75	11
	> 3.75%	2	14
Non-events	≤ 3.75%	4434	84
	> 3.75%	30	148

eFigure 3 caption: Panel A presents net reclassification improvement (NRI) from the addition of polygenic scores to the traditional risk model for each ASCVD outcome, stratified by ancestry and age group. Panels B to E contain

reclassification tables for all ancestries combined, stratified by age group. Rows refer to predicted 5-year risk categories from the traditional risk model, and columns refer to predicted risk from the combined traditional and polygenic risk score model. Blue cells indicate correct reclassifications: i.e. the GxE model predicted a higher risk group, compared to the traditional model, for a patient who experienced an event, or a lower risk group for a non-event. Orange shaded cells highlight incorrect reclassifications. The traditional model includes age, sex, and 5 principal components of genetic ancestry (to be comparable to the genetic model), and the risk cutoff (>3.75%) represents a clinically relevant 5-year risk. Among ASCVD events in the youngest subgroup (ages < 40, panel E), the net proportion of correct reclassifications was NRI+ = (11-2)/102 = 8.82%, and among non-events was NRI- = (30-84)/4696 = -1.15%. The overall net reclassification index is defined as the sum of the net reclassification proportions for events and nonevents (NRI = 8.82% + -1.15% = 7.67%).
Key: Estimates and 95% confidence intervals are shown for White (black, triangle), Black (red, circle), and Hispanic (blue, square) population groups.