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A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease

In the format provided by the authors and unedited

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Table 1: GPS_{Mult} inputs and parameters

Trait	Name	Dominant Ancestry	N Cases	N Controls	ρ	h^2 scale	Is sparse LD	Train OR/SD	Layer 1 Mixing weight	Layer 2 Mixing weight	Final Weight	Reference
CAD	CARDIO-GRAM plusC4D no UKBB	EUR	86847	417789	0.018	1	F	1.92	0.51	0.67	0.263	[1]
	BBJ	EAS	29319	183134	0.01	0.7	F	1.43	0.08		0.041	[2]
	Genes & Health	SAS	1110	20898	0.0056	1.4	F	1.11	0.05		0.026	[3]
	FinnGen	EUR	33628	275526	0.0032	1.4	F	1.46	0.02		0.010	[4]
	MVP	EUR	95151	197287	0.018	0.7	F	1.72	0.23		0.120	[5]
	MVP	AFR	17202	59507	0.018	1.4	F	1.10	0.01		0.006	[5]
	MVP	HISP	6378	24270	0.0018	0.7	F	1.16	0.00		0.000	[5]
BMI	GIANT	EUR	339224		1	1	T	1.12	0.11	0.03	0.014	[6]
	BBJ	EAS	163835		0.32	0.7	F	1.06	0.05		0.007	[2]
DBP	MVP	EUR	249262		0.032	1.4	F	1.11	0.12	0.08	0.038	[7]
	BBJ	EAS	145515		0.01	0.7	F	1.07	0.06		0.019	[2]
SBP	MVP	EUR	249262		0.032	0.7	F	1.19	0.19	0.00	0.000	[7]
	BBJ	EAS	145505		0.018	1.4	F	1.09	0.05		0.000	[2]
DM	Diamante/ MVP	EUR	148726	965732	1	1.4	T	1.31	0.29	0.33	0.179	[8]

	MVP	AFR	24646	31446	0.018	0.7	F	1.06	0.00		0.000	[8]
	MVP	HISP	8,616	11,829	0.032	1.4	T	1.09	0.04		0.027	[8]
	AGEN T2D	EAS	77418	356122	0.56	1	T	1.14	0.01		0.005	[9]
	FinnGen	EUR	49303	255466	0.032	1.4	F	1.16	0.03		0.018	[4]
	Genes & Health	SAS	9044	12066	0.0056	1.4	F	1.05	0.00		0.000	[10]
LDL-C	GLGC	EUR	1320016		0.1	0.7	T	1.22	0.26	0.09	0.028	[11]
	GLGC	AFR	99432		0.01	0.7	T	1.15	0.07		0.007	[11]
	GLGC	SAS	40963		0.00032	1.4	T	1.15	0.00		0.000	[11]
	MVP	EUR	215551		0.01	0.7	T	1.17	0.14		0.015	[12]
	MVP	AFR	57332		0.0056	0.7	T	1.13	0.05		0.005	[12]
	MVP	HISP	24742		0.0018	0.7	T	1.18	0.09		0.009	[12]
	BBJ	EAS	72866		0.0032	0.7	T	1.13	0.00		0.000	[2]
HDL-C	GLGC	EUR	1320016		1	0.7	T	1.24	0.07	0.06	0.009	[11]
	GLGC	AFR	99432		0.32	1.4	F	1.08	0.00		0.000	[11]
	GLGC	SAS	40963		0.001	1	T	1.05	0.04		0.006	[11]
	MVP	EUR	215551		0.32	1	F	1.20	0.20		0.026	[12]
	MVP	AFR	57332		0.0056	1	F	1.07	0.00		0.000	[12]

	MVP	HISP	23946		0.056	1.4	F	1.08	0.00		0.000	[12]
	BBJ	EAS	74970		0.32	0.7	F	1.06	0.00		0.000	[2]
	GLGC	EUR	1320016		1	0.7	T	1.24	0.24		0.000	[11]
	GLGC	AFR	99432		0.018	1.4	F	1.09	0.00		0.000	[11]
	GLGC	SAS	40963		0.01	0.7	F	1.09	0.00		0.000	[11]
	MVP	EUR	215551		0.18	1	F	1.19	0.00		0.000	[12]
	MVP	AFR	57332		0.032	0.7	F	1.07	0.00		0.000	[12]
	MVP	HISP	24063		0.018	1.4	F	1.08	0.00		0.000	[12]
TG	BBJ	EAS	111667		0.056	0.7	T	1.07	0.00	0.00	0.000	[2]
	MVP	EUR	24009	150983	0.01	0.7	F	1.32	0.25		0.012	[13]
	MVP	AFR	5273	42485	1	1.4	T	1.07	0.05		0.002	[13]
	MVP	HISP	1925	18285	0.0032	1.4	T	1.07	0.03		0.002	[13]
	FinnGen	EUR	11924	288638	0.0056	0.7	F	1.16	0.08		0.004	[4]
PAD	BBJ	EAS	4112	173601	0.0032	0.7	F	1.13	0.09	0.04	0.004	[2]
	MEGA-STROKE	EUR	40585	406111	0.0032	0.7	T	1.17	0.17		0.030	[14]
	BBJ	EAS	22664	152022	0.56	1.4	T	1.06	0.05		0.010	[2]
Stroke	GBMI	AFR	1161	24416	0.018	1.4	T	1.04	0.05	0.07	0.010	[15]
CKD	MVP	EUR	223386		0.0001	0.7	T	1.05	0.04	0.06	0.025	[16]

	MVP	AFR	57336	0.018	1	F	1.04	0.03		0.019	[16]
	BBJ	EAS	150266	0.0056	0.7	T	1.02	0.00		0.000	[2]

Traits: CAD – coronary artery disease; BMI – body mass index; DBP – diastolic blood pressure; SBP – systolic blood pressure; DM – diabetes mellitus; LDL-C – low density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; PAD – peripheral artery disease; CKD – chronic kidney disease.
Consortia: CARDIOGRAMplusC4D no UKBB – Coronary ARtery DIsease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics consortium excluding UK Biobank; BBJ – Biobank Japan; GIANT – Genetic Investigation of ANthropometric Traits; MVP – Million Veteran Program; AGEN-T2D – Asian Genetic Epidemiology Network Type 2 Diabetes Consortium; GLGC – Global Lipids Genetics Consortium excluding the UK Biobank; GBMI – Global Biobank Meta-analysis Initiative
Ancestries: AFR – African; EAS – East Asian; EUR – European; SAS – South Asian
LDPred2 parameters: ρ – tuning parameter to model the proportion of variants assumed to be causal; h^2 scale – factor by which heritability is scaled; is sparse LD – whether a sparse linkage disequilibrium matrix is applied, if true some variant effect estimates are fit to zero. A total of 102 combinations of these three parameters were possible and led to generation of 102 polygenic scores for each input ancestry-stratified set of GWAS summary statistics. The parameters leading to the best individually performing polygenic score in predicting CAD in a training dataset of 116,649 participants in the UK Biobank were chosen, specific to each ancestry-specific GWAS.
Mixing weights: Layer 1 – weight determined from a logistic regression model predicting CAD in a UK Biobank training dataset by combining different ancestry-specific GPS from GWAS for a specific trait. Layer 2 - weight determined from a logistic regression model predicting CAD in the same UKB training dataset by combining different multi-ancestry trait-specific scores from the Layer 1 step. Final weight - overall mixing weight incorporating proportional weights from layers 1 and 2, normalized to 100%. The final GPS_{Mult} score was a linear combination of all the input scores according to the final weight. The dataset for training the models and for estimating the mixing weight was from 116,649 participants in the UK Biobank. All the regression models for predicting CAD were adjusted for age, sex, genotyping array, and the first ten principal components of ancestry.

Table 2: Summary of GPS_{Mult} training and validation datasets

Stage	Training		Validation						
Cohort	UK Biobank	UK Biobank				MVP			G&H
Ancestry	European	African	East Asian	European	South Asian	African	European	Hispanic	South Asian
N	116649	7281	1464	308264	8982	33096	124467	16433	16874
Age (SD)	57.5 (7.9)	52.4 (8.0)	53.0 (7.6)	57.3 (8.0)	53.8 (8.5)	56.1 (12.4)	60.8 (13.3)	51.9 (15.5)	40.6 (14.5)
Male Sex (%)	47.5%	43.5%	37.2%	45.6%	54.1%	84.1%	91.3%	87.7%	45.9%
Case	4412	124	22	10492	542	4831	29171	2140	853
Control	112237	7157	1442	297772	8440	28265	95296	14293	16021

Baseline demographics of participants included in GPS_{Mult} training and validation. These individuals were not included in genome-wide association data used to construct GPS_{Mult}, and individuals in training and validation of GPS_{Mult} are distinct. MVP: Million Veteran Program; G&H: Genes & Health. SD: Standard deviation

Table 3: Performance of polygenic scores for CAD from Polygenic Score Catalog in the UK Biobank Study

Score Name	Identifier	Publication	OR/SD [95% CI]	P	Population
GRS28	PGS000200	Tikkanen E et al. Arterioscler Thromb Vasc Biol (2013)	1.31 [1.31-1.34]	$<2x10^{-16}$	EUR
GRS27	PGS000010	Mega JL et al. Lancet (2015)	1.35 [1.35-1.38]	$<2x10^{-16}$	EUR
GRS50	PGS000011	Tada H et al. Eur Heart J (2015)	1.34 [1.34-1.37]	$<2x10^{-16}$	EUR
GRS49K	PGS000012	Abraham G et al. Eur Heart J (2016)	1.44 [1.44-1.47]	$<2x10^{-16}$	EUR
CHD57	PGS000057	Natarajan P et al. Circulation (2017)	1.34 [1.34-1.37]	$<2x10^{-16}$	EUR
GRS_CAD	PGS000019	Paquette M et al. J Clin Lipidol (2017)	1.49 [1.49-1.52]	$<2x10^{-16}$	EUR
GPS_{2018}	PGS000013	Khera AV et al. Nat Genet (2018)	1.72 [1.72-1.76]	$<2x10^{-16}$	EUR
metaGRS_CAD	PGS000018	Inouye M et al. J Am Coll Cardiol (2018)	1.77 [1.77-1.8]	$<2x10^{-16}$	EUR
CHD46	PGS000059	Hajek C et al. Circ Genom Precis Med (2018)	1.27 [1.27-1.3]	$<2x10^{-16}$	EUR
CAD_EJ2020	PGS000116	Elliott J et al. JAMA (2020)	1.53 [1.53-1.56]	$<2x10^{-16}$	EUR
PRS_COMBINED	PGS000749	Gola D et al. Circ Genom Precis Med (2020)	1.49 [1.49-1.52]	$<2x10^{-16}$	EUR
PRS_CHD	PGS000329	Mars N et al. Nat Med (2020)	1.64 [1.64-1.68]	$<2x10^{-16}$	EUR
GPS_CAD_SA	PGS000296	Wang M et al. J Am Coll Cardiol (2020)	1.67 [1.67-1.71]	$<2x10^{-16}$	EUR
PRS70_CAD	PGS000349	Pechlivanis S et al. BMC Med Genet (2020)	1.14 [1.14-1.17]	$<2x10^{-16}$	EUR
GRS_Metabo	PGS000818	Bauer A et al. Genet Epidemiol (2021)	1.48 [1.48-1.51]	$<2x10^{-16}$	EUR
$AnnoPred_{CAD}$	PGS001355	Ye Y et al. Circ Genom Precis Med (2021)	1.76 [1.76-1.8]	$<2x10^{-16}$	EUR
metaPRS_CAD	PGS002262	Lu X et al. Eur Heart J (2022)	1.30 [1.3-1.32]	$<2x10^{-16}$	EUR

CHD_PRSCS	PGS001780	Tamlander M et al. Commun Biol (2022)	1.73 [1.73-1.77]	$<2x10^{-16}$	EUR
GPS_{Mult}	-	-	2.14 [2.10-2.19]	$<2x10^{-16}$	EUR

A series of prior published scores or CAD from the Polygenic Score Catalog that did not include any UK Biobank participants in the GWAS data for score development were compared with GPS_{Mult} within the validation cohort of European ancestry individuals from the UK Biobank. The odds ratio for prevalent coronary artery disease (CAD) risk per standard deviation (ORS/SD) of the polygenic score and 95% confidence interval were assessed in a logistic regression model adjusted for age, sex, genotyping array, and the first ten principal components of ancestry. *P* values are derived from a *t*-test implemented in the GLM function in R and are two-sided. Beta: Effect size from logistic regression; SE: standard error.

Table 4: Baseline risk factor distributions and correlations with GPS_{Mult}

	Prevalent CAD	Incident CAD	No CAD	All	Correlation
N	11180	11898	302913	325991	
LDL Cholesterol* (mg/dl, mean (SD))	143.78 (35.76)	156.08 (35.81)	145.25 (32.95)	145.60 (33.22)	0.152
HDL Cholesterol* (mg/dl, mean (SD))	46.20 (12.16)	50.49 (13.19)	56.72 (14.81)	56.13 (14.84)	-0.115
Triglycerides* (mg/dl, median [IQR])	170.17 [118.87, 243.84]	167.25 [117.68, 241.03]	131.98 [92.65, 192.47]	134.37 [93.98, 196.19]	0.108
Systolic Blood Pressure (mm Hg, mean (SD))	140.00 (19.86)	147.28 (20.06)	139.37 (19.56)	139.68 (19.64)	0.081
Diastolic Blood Pressure (mm Hg, mean (SD))	78.94 (10.93)	84.57 (10.94)	82.27 (10.66)	82.24 (10.71)	0.071
Body-mass Index (kg/m^2, mean (SD))	29.13 (4.77)	28.58 (4.79)	27.26 (4.74)	27.37 (4.76)	0.108
Diabetes Mellitus# (%)	2197 (19.7)	1460 (12.3)	14012 (4.6)	17669 (5.4)	0.028
Chronic Kidney Disease# (%)	1621 (15.2)	1134 (10.0)	11484 (4.0)	14239 (4.6)	0.091

The baseline variable distributions for traditional coronary artery disease (CAD) risk factors stratified by CAD case status. Correlations between the GPS_{Mult} and risk factors across the population, adjusted for top 10 principal components and traditional risk factors were assessed using Pearson's correlation for continuous traits and #point biserial correlation for binary traits. The P value for each association was less than 2×10^{-12}. *LDL-C, HDL-C, and triglyceride values adjusted if individual taking cholesterol lowering medications as described in Patel et al. *JAMA Network Open* 2020.[17] For example, in the case of statin intake, lower density cholesterol was divided by 0.7 and triglycerides by 0.85. Diagnosis of diabetes was based on self-report, primary care records or hospitalization records confirming a clinical diagnosis, self-reported consumption of medications to treat diabetes, or glycohemoglobin >6.5% at enrollment and chronic kidney disease was defined as eGFRcys <60 mL/min, as previously described.[18]

Table 5: Baseline characteristics according to high GPS_{Mult}

	Bottom 80% GPS_{Mult}	Top 20% GPS_{Mult}
Number of individuals	224,292	56,424
Prevalent coronary artery disease (%)	5,496 (2.5)	4,155 (7.4)
Age, years (mean, SD)	57.5 (7.9)	57.2 (9.0)
Male sex (%)	102,639 (45.8)	25,926 (45.9)
Hypertension (%)	58,635 (27.2)	20,305 (37.9)
Diabetes Mellitus (%)	9,219 (4.1)	4,653 (8.2)
*LDL cholesterol, mg/dL (mean (SD))	137.7 (33.0)	140.5 (35.9)
*HDL cholesterol, mg/dL (mean (SD))	57.0 (14.9)	53.9 (14.3)
*Triglycerides, mg/dL (median [IQR])	129.4 [91.6, 186.8]	142.3 [100.7, 204.9]
Current smoking (%)	20,365 (9.1)	5,866 (10.4)
Family history of heart disease (%)	95,049 (42.4)	29,936 (53.1)
Body mass index, kg/m^2 (mean (SD))	27.2 (4.7)	28.1 (5.0)
Lipid-lowering therapy (%)	31,201 (13.9)	13,892 (24.6)

Baseline characteristics according to high GPS_{Mult} status, defined as the top 20% of the distribution empirically shown to be at ≥3-fold risk of coronary artery disease. LDL: low-density lipoprotein; HDL: high-density lipoprotein. *LDL-C, HDL-C, and triglyceride values were adjusted for cholesterol-lowering medication status, as previously described.[17]

Table 6: Performance of polygenic scores for CAD from Polygenic Score Catalog in the Million Veteran Program Study

Score Name	Identifier	Publication	Beta	SE	P	OR/SD [95% CI]	Population
GRS28	PGS000200	Tikkanen E et al. Arterioscler Thromb Vasc Biol (2013)	0.053	0.016	1.20E-03	1.05 (1.02-1.09)	AFR
GRS27	PGS000010	Mega JL et al. Lancet (2015)	0.066	0.016	4.60E-05	1.07 (1.04-1.1)	AFR
GRS50	PGS000011	Tada H et al. Eur Heart J (2015)	0.073	0.016	6.30E-06	1.08 (1.04-1.11)	AFR
GRS49K	PGS000012	Abraham G et al. Eur Heart J (2016)	0.082	0.016	4.70E-07	1.09 (1.05-1.12)	AFR
CHD57	PGS000057	Natarajan P et al. Circulation (2017)	0.066	0.016	6.20E-05	1.07 (1.03-1.1)	AFR
GRS_CAD	PGS000019	Paquette M et al. J Clin Lipidol (2017)	0.115	0.016	2.60E-12	1.12 (1.09-1.16)	AFR
GPS_{2018}	PGS000013	Khera AV et al. Nat Genet (2018)	0.128	0.016	3.10E-15	1.14 (1.1-1.17)	AFR
CAD_GRS_204	PGS000058	Morieri ML et al. Diabetes Care (2018)	0.117	0.016	1.10E-12	1.12 (1.09-1.16)	AFR
metaGRS_CAD	PGS000018	Inouye M et al. J Am Coll Cardiol (2018)	0.155	0.016	2.60E-21	1.17 (1.13-1.21)	AFR
CHD46	PGS000059	Hajek C et al. Circ Genom Precis Med (2018)	0.060	0.016	2.20E-04	1.06 (1.03-1.1)	AFR
157SNP_GRS	PGS000798	Severance LM et al. J Cardiovasc Comput Tomogr (2019)	0.086	0.016	1.30E-07	1.09 (1.06-1.13)	AFR
CAD_EJ2020	PGS000116	Elliott J et al. JAMA (2020)	0.114	0.016	4.30E-12	1.12 (1.08-1.16)	AFR
PRS_DE	PGS000748	Gola D et al. Circ Genom Precis Med (2020)	0.118	0.016	3.20E-13	1.13 (1.09-1.16)	AFR
PRS_COMBINED	PGS000749	Gola D et al. Circ Genom Precis Med (2020)	0.112	0.016	4.50E-12	1.12 (1.08-1.16)	AFR
PRS_CHD	PGS000329	Mars N et al. Nat Med (2020)	0.144	0.016	1.00E-18	1.15 (1.12-1.19)	AFR
GPS_CAD_SA	PGS000296	Wang M et al. J Am Coll Cardiol (2020)	0.158	0.016	2.50E-22	1.17 (1.13-1.21)	AFR
PRS70_CAD	PGS000349	Pechlivanis S et al. BMC Med Genet (2020)	0.028	0.016	8.10E-02	1.03 (1-1.06)	AFR
$MetaPRS_{CAD}$	PGS000337	Koyama S et al. Nat Genet (2020)	0.167	0.016	3.00E-24	1.18 (1.14-1.22)	AFR
PRS176_CHD	PGS000899	Feitosa MF et al. Circ Genom Precis Med (2021)	0.109	0.016	3.40E-11	1.11 (1.08-1.15)	AFR

GRS_Metabo	PGS000818	Bauer A et al. Genet Epidemiol (2021)	0.101	0.016	6.80E-10	1.11 (1.07-1.14)	AFR
AnnoPred$_{CAD}$	PGS001355	Ye Y et al. Circ Genom Precis Med (2021)	0.161	0.016	5.10E-23	1.18 (1.14-1.21)	AFR
portability-ldpred2	PGS002048	Prive F et al. Am J Hum Genet (2022)	0.129	0.016	5.30E-15	1.14 (1.1-1.17)	AFR
metaPRS_CAD	PGS002262	Lu X et al. Eur Heart J (2022)	0.061	0.016	2.10E-04	1.06 (1.03-1.1)	AFR
PRSCS$_{CHD}$	PGS001780	Tamlander M et al. Commun Biol (2022)	0.166	0.016	5.40E-24	1.18 (1.14-1.22)	AFR
GBE_HC942	PGS000962	Tanigawa Y et al. PLoS Genet (2022)	0.088	0.016	6.60E-08	1.09 (1.06-1.13)	AFR
ldpred_cad	PGS002244	Mars N et al. Cell Genom (2022)	0.139	0.016	1.70E-17	1.15 (1.11-1.19)	AFR
PRS_2022	PGS003356	Aragam KA et al. Nat Genet (2022)	0.160	0.016	1.10E-22	1.17 (1.14-1.21)	AFR
GPSMult	-	-	0.222	0.016	2.20E-41	1.25 (1.21-1.29)	AFR
GRS28	PGS000200	Tikkanen E et al. Arterioscler Thromb Vasc Biol (2013)	0.185	0.007	7.50E-148	1.2 (1.19-1.22)	EUR
GRS27	PGS000010	Mega JL et al. Lancet (2015)	0.214	0.007	4.40E-199	1.24 (1.22-1.26)	EUR
GRS50	PGS000011	Tada H et al. Eur Heart J (2015)	0.195	0.007	5.80E-163	1.21 (1.2-1.23)	EUR
GRS49K	PGS000012	Abraham G et al. Eur Heart J (2016)	0.249	0.007	4.80E-262	1.28 (1.27-1.3)	EUR
CHD57	PGS000057	Natarajan P et al. Circulation (2017)	0.118	0.007	8.80E-62	1.13 (1.11-1.14)	EUR
GRS_CAD	PGS000019	Paquette M et al. J Clin Lipidol (2017)	0.273	0.007	1.1E-312	1.31 (1.3-1.33)	EUR
GPS_CAD	PGS000013	Khera AV et al. Nat Genet (2018)	0.370	0.007	5.6E-551	1.45 (1.43-1.47)	EUR
CAD_GRS_204	PGS000058	Morieri ML et al. Diabetes Care (2018)	0.326	0.007	8.4E-439	1.39 (1.37-1.41)	EUR
metaGRS_CAD	PGS000018	Inouye M et al. J Am Coll Cardiol (2018)	0.385	0.007	1.2E-593	1.47 (1.45-1.49)	EUR
CHD46	PGS000059	Hajek C et al. Circ Genom Precis Med (2018)	0.165	0.007	1.00E-118	1.18 (1.16-1.2)	EUR
157SNP_GRS	PGS000798	Severance LM et al. J Cardiovasc Comput Tomogr (2019)	0.289	0.007	4.0E-347	1.33 (1.32-1.35)	EUR
CAD_EJ2020	PGS000116	Elliott J et al. JAMA (2020)	0.295	0.007	6.0E-359	1.34 (1.32-1.36)	EUR
PRS_DE	PGS000748	Gola D et al. Circ Genom Precis Med (2020)	0.273	0.007	3.1E-312	1.31 (1.3-1.33)	EUR

PRS_COMBINED	PGS000749	Gola D et al. Circ Genom Precis Med (2020)	0.275	0.007	2.9E-316	1.32 (1.3-1.33)	EUR
PRS_CHD	PGS000329	Mars N et al. Nat Med (2020)	0.367	0.007	1.5E-551	1.44 (1.42-1.46)	EUR
GPS_CAD_SA	PGS000296	Wang M et al. J Am Coll Cardiol (2020)	0.356	0.007	2.7E-515	1.43 (1.41-1.45)	EUR
PRS70_CAD	PGS000349	Pechlivanis S et al. BMC Med Genet (2020)	0.104	0.007	1.30E-48	1.11 (1.09-1.13)	EUR
$MetaPRS_{CAD}$	PGS000337	Koyama S et al. Nat Genet (2020)	0.418	0.007	1.5E-688	1.52 (1.5-1.54)	EUR
PRS176_CHD	PGS000899	Feitosa MF et al. Circ Genom Precis Med (2021)	0.327	0.007	2.8E-441	1.39 (1.37-1.41)	EUR
GRS_Metabo	PGS000818	Bauer A et al. Genet Epidemiol (2021)	0.258	0.007	1.80E-279	1.29 (1.28-1.31)	EUR
$AnnoPred_{CAD}$	PGS001355	Ye Y et al. Circ Genom Precis Med (2021)	0.383	0.007	7.3E-585	1.47 (1.45-1.49)	EUR
portability-ldpred2	PGS002048	Prive F et al. Am J Hum Genet (2022)	0.379	0.007	2.0E-580	1.46 (1.44-1.48)	EUR
metaPRS_CAD	PGS002262	Lu X et al. Eur Heart J (2022)	0.207	0.007	2.00E-182	1.23 (1.21-1.25)	EUR
$PRSCS_{CHD}$	PGS001780	Tamlander M et al. Commun Biol (2022)	0.372	0.007	3.9E-556	1.45 (1.43-1.47)	EUR
GBE_HC942	PGS000962	Tanigawa Y et al. PLoS Genet (2022)	0.287	0.007	6.2E-345	1.33 (1.31-1.35)	EUR
ldpred_cad	PGS002244	Mars N et al. Cell Genom (2022)	0.344	0.007	4.3E-482	1.41 (1.39-1.43)	EUR
PRS_{2022}	PGS003356	Aragam KA et al. Nat Genet (2022)	0.477	0.008	1.4E-874	1.61 (1.59-1.64)	EUR
GPS_{Mult}	-	-	0.542	0.008	1.1E-1085	1.72 (1.69-1.75)	EUR
GRS28	PGS000200	Tikkanen E et al. Arterioscler Thromb Vasc Biol (2013)	0.123	0.025	1.10E-06	1.13 (1.08-1.19)	HIS
GRS27	PGS000010	Mega JL et al. Lancet (2015)	0.147	0.025	5.70E-09	1.16 (1.1-1.22)	HIS
GRS50	PGS000011	Tada H et al. Eur Heart J (2015)	0.136	0.025	8.20E-08	1.15 (1.09-1.2)	HIS
GRS49K	PGS000012	Abraham G et al. Eur Heart J (2016)	0.217	0.025	1.40E-17	1.24 (1.18-1.31)	HIS
CHD57	PGS000057	Natarajan P et al. Circulation (2017)	0.127	0.025	5.10E-07	1.14 (1.08-1.19)	HIS
GRS_CAD	PGS000019	Paquette M et al. J Clin Lipidol (2017)	0.236	0.025	9.70E-21	1.27 (1.2-1.33)	HIS
GPS_{2018}	PGS000013	Khera AV et al. Nat Genet (2018)	0.286	0.026	9.50E-29	1.33 (1.27-1.4)	HIS

CAD_GRS_204	PGS000058	Morieri ML et al. Diabetes Care (2018)	0.286	0.026	6.60E-29	1.33 (1.27-1.4)	HIS
metaGRS_CAD	PGS000018	Inouye M et al. J Am Coll Cardiol (2018)	0.320	0.025	2.90E-36	1.38 (1.31-1.45)	HIS
CHD46	PGS000059	Hajek C et al. Circ Genom Precis Med (2018)	0.159	0.025	3.50E-10	1.17 (1.12-1.23)	HIS
157SNP_GRS	PGS000798	Severance LM et al. J Cardiovasc Comput Tomogr (2019)	0.244	0.025	9.10E-22	1.28 (1.21-1.34)	HIS
CAD_EJ2020	PGS000116	Elliott J et al. JAMA (2020)	0.251	0.026	1.10E-22	1.29 (1.22-1.35)	HIS
PRS_DE	PGS000748	Gola D et al. Circ Genom Precis Med (2020)	0.254	0.025	9.80E-24	1.29 (1.23-1.36)	HIS
PRS_COMBINED	PGS000749	Gola D et al. Circ Genom Precis Med (2020)	0.238	0.025	4.40E-21	1.27 (1.21-1.33)	HIS
PRS_CHD	PGS000329	Mars N et al. Nat Med (2020)	0.285	0.025	4.50E-29	1.33 (1.27-1.4)	HIS
GPS_CAD_SA	PGS000296	Wang M et al. J Am Coll Cardiol (2020)	0.291	0.026	4.50E-30	1.34 (1.27-1.41)	HIS
PRS70_CAD	PGS000349	Pechlivanis S et al. BMC Med Genet (2020)	0.091	0.025	2.90E-04	1.1 (1.04-1.15)	HIS
$MetaPRS_{CAD}$	PGS000337	Koyama S et al. Nat Genet (2020)	0.398	0.026	2.30E-52	1.49 (1.41-1.57)	HIS
PRS176_CHD	PGS000899	Feitosa MF et al. Circ Genom Precis Med (2021)	0.280	0.026	6.30E-28	1.32 (1.26-1.39)	HIS
GRS_Metabo	PGS000818	Bauer A et al. Genet Epidemiol (2021)	0.218	0.025	1.40E-17	1.24 (1.18-1.31)	HIS
$AnnoPred_{CAD}$	PGS001355	Ye Y et al. Circ Genom Precis Med (2021)	0.349	0.026	1.10E-41	1.42 (1.35-1.49)	HIS
portability-ldpred2	PGS002048	Prive F et al. Am J Hum Genet (2022)	0.337	0.026	2.40E-39	1.4 (1.33-1.47)	HIS
metaPRS_CAD	PGS002262	Lu X et al. Eur Heart J (2022)	0.202	0.025	2.60E-15	1.22 (1.16-1.29)	HIS
$PRSCS_{CHD}$	PGS001780	Tamlander M et al. Commun Biol (2022)	0.330	0.026	1.50E-37	1.39 (1.32-1.46)	HIS
GBE_HC942	PGS000962	Tanigawa Y et al. PLoS Genet (2022)	0.222	0.025	2.30E-18	1.25 (1.19-1.31)	HIS
ldpred_cad	PGS002244	Mars N et al. Cell Genom (2022)	0.269	0.026	4.60E-26	1.31 (1.25-1.38)	HIS
PRS_2022	PGS003356	Aragam KA et al. Nat Genet (2022)	0.418	0.026	1.40E-57	1.52 (1.44-1.6)	HIS
GPSMult	-	-	0.477	0.027	5.10E-72	1.61 (1.53-1.7)	HIS

The odds ratio for prevalent coronary artery disease (CAD) risk per standard deviation (OR/SD) of the polygenic score and 95% confidence interval were validated in a logistic regression model adjusted for age, sex, genotyping array, and the first ten principal components of ancestry

in a holdout cohort of individuals of the Million Veteran Project using prior published scores from the Polygenic Score Catalog. *P* values are derived from a *t*-test implemented in the GLM function in R and are two-sided. Beta: Effect size from logistic regression; SE: standard error. AFR: African ancestry; EUR: European ancestry; HISP: Hispanic ancestry.

Table 7: Performance of polygenic scores for CAD from Polygenic Score Catalog in the Genes & Health Study

Score Name	Identifier	Publication	Beta	SE	P	OR/SD [95% CI]	Population
GRS28	PGS000200	Tikkanen E et al. Arterioscler Thromb Vasc Biol (2013)	0.169	0.040	2.40E-05	1.18 [1.09-1.28]	SAS
GRS27	PGS000010	Mega JL et al. Lancet (2015)	0.159	0.040	6.79E-05	1.17 [1.08-1.27]	SAS
GRS50	PGS000011	Tada H et al. Eur Heart J (2015)	0.108	0.039	5.91E-03	1.11 [1.03-1.2]	SAS
GRS49K	PGS000012	Abraham G et al. Eur Heart J (2016)	0.288	0.044	4.38E-11	1.33 [1.22-1.45]	SAS
CHD57	PGS000057	Natarajan P et al. Circulation (2017)	0.105	0.040	9.17E-03	1.11 [1.03-1.2]	SAS
GRS_CAD	PGS000019	Paquette M et al. J Clin Lipidol (2017)	0.218	0.040	4.99E-08	1.24 [1.15-1.34]	SAS
GPS_{2018}	PGS000013	Khera AV et al. Nat Genet (2018)	0.285	0.042	7.74E-12	1.33 [1.23-1.44]	SAS
CAD_GRS_204	PGS000058	Morieri ML et al. Diabetes Care (2018)	0.229	0.040	1.23E-08	1.26 [1.16-1.36]	SAS
metaGRS_CAD	PGS000018	Inouye M et al. J Am Coll Cardiol (2018)	0.327	0.044	9.81E-14	1.39 [1.27-1.51]	SAS
CHD46	PGS000059	Hajek C et al. Circ Genom Precis Med (2018)	0.111	0.040	5.83E-03	1.12 [1.03-1.21]	SAS
157SNP_GRS	PGS000798	Severance LM et al. J Cardiovasc Comput Tomogr (2019)	0.244	0.041	2.07E-09	1.28 [1.18-1.38]	SAS
CAD_EJ2020	PGS000116	Elliott J et al. JAMA (2020)	0.327	0.042	4.18E-15	1.39 [1.28-1.5]	SAS
PRS_COMBINED	PGS000749	Gola D et al. Circ Genom Precis Med (2020)	0.328	0.041	2.26E-15	1.39 [1.28-1.51]	SAS
PRS_DE	PGS000748	Gola D et al. Circ Genom Precis Med (2020)	0.306	0.041	1.13E-13	1.36 [1.25-1.47]	SAS
PRS_CHD	PGS000329	Mars N et al. Nat Med (2020)	0.310	0.041	2.26E-14	1.36 [1.26-1.48]	SAS
GPS_CAD_SA	PGS000296	Wang M et al. J Am Coll Cardiol (2020)	0.338	0.041	3.57E-16	1.4 [1.29-1.52]	SAS
PRS70_CAD	PGS000349	Pechlivanis S et al. BMC Med Genet (2020)	0.072	0.040	6.87E-02	1.08 [0.99-1.16]	SAS
$MetaPRS_{CAD}$	PGS000337	Koyama S et al. Nat Genet (2020)	0.428	0.042	1.17E-24	1.53 [1.41-1.67]	SAS
PRS176_CHD	PGS000899	Feitosa MF et al. Circ Genom Precis Med (2021)	0.251	0.041	5.86E-10	1.29 [1.19-1.39]	SAS
GRS_Metabo	PGS000818	Bauer A et al. Genet Epidemiol (2021)	0.209	0.040	2.13E-07	1.23 [1.14-1.33]	SAS

CAD_AnnoPred	PGS001355	Ye Y et al. Circ Genom Precis Med (2021)	0.352	0.041	1.71E-17	1.42 [1.31-1.54]	SAS
portability-ldpred2	PGS002048	Priv√© F et al. Am J Hum Genet (2022)	0.380	0.041	4.53E-20	1.46 [1.35-1.59]	SAS
metaPRS_CAD	PGS002262	Lu X et al. Eur Heart J (2022)	0.193	0.041	6.24E-06	1.21 [1.12-1.31]	SAS
$PRSCS_{CHD}$	PGS001780	Tamlander M et al. Commun Biol (2022)	0.420	0.042	3.64E-23	1.52 [1.4-1.65]	SAS
GBE_HC942	PGS000962	Tanigawa Y et al. PLoS Genet (2022)	0.180	0.040	2.69E-06	1.2 [1.11-1.29]	SAS
ldpred_cad	PGS002244	Mars N et al. Cell Genom (2022)	0.301	0.042	4.13E-13	1.35 [1.25-1.47]	SAS
PRS_{2022}	PGS003356	Aragam KA et al. Nat Genet (2022)	0.469	0.042	1.37E-29	1.6 [1.47-1.73]	SAS
GPS_{Mult}	-	-	0.606	0.042	1.95E-47	1.83 [1.69-1.99]	SAS

The odds ratio for prevalent coronary artery disease (CAD) risk per standard deviation (OR/SD) of the polygenic score and 95% confidence interval were validated in a logistic regression model adjusted for age, sex, genotyping array, and the first ten principal components of ancestry in a holdout cohort of individuals of the Genes & Health study using prior published scores from the Polygenic Score Catalog. *P* values are derived from a *t*-test implemented in the GLM function in R and are two-sided. Beta: Effect size from logistic regression; SE: standard error. SAS: South Asian ancestry.

Table 8: Model C-statistics by ancestry in the UK Biobank Study

Ancestry	All	African	East Asian	European	South Asian
Age+Sex	0.71 (0.706-0.715)	0.708 (0.666-0.75)	0.775 (0.694-0.856)	0.708 (0.703-0.712)	0.712 (0.692-0.732)
PCE	0.739 (0.735-0.744)	0.749 (0.707-0.791)	0.803 (0.71-0.895)	0.739 (0.734-0.743)	0.739 (0.717-0.76)
PCE+GPS_{Mult}+PCE*GPS_{Mult}	0.763 (0.759-0.768)	0.753 (0.712-0.794)	0.882 (0.843-0.921)	0.762 (0.758-0.767)	0.764 (0.743-0.784)
QRISK3	0.746 (0.741-0.75)	0.747 (0.698-0.796)	0.811 (0.73-0.893)	0.744 (0.74-0.749)	0.745 (0.722-0.769)
QRISK3+GPS_{Mult}+QRISK3*GPS_{Mult}	0.769 (0.764-0.773)	0.759 (0.712-0.806)	0.882 (0.834-0.929)	0.768 (0.763-0.772)	0.777 (0.756-0.799)

C-statistics stratified by ancestry are based on 10-year follow-up events from Cox regression models of listed variables, the first ten principal components of genetic ancestry, and genotyping array. ACC/AHA Pooled Cohort Equations (PCE) and QISK3 10-year risk estimates include age and sex variables in their risk estimation.

Table 9: Model net reclassification by ancestry in the UK Biobank Study

NRI		Status	All	African	East Asian	European	South Asian
Categorical	PCE	Full	0.070 (0.059-0.082)	0.010 (-0.016-0.035)	0.000 (-0.008-0.176)	0.073 (0.063-0.081)	0.067 (0.019-0.147)
		Cases	0.081 (0.069-0.094)	0.010 (-0.016-0.034)	0.000 (0.000-0.179)	0.083 (0.074-0.092)	0.102 (0.043-0.188)
		Noncases	-0.011 (-0.012 - -0.009)	0.00 (-0.003-0.002)	0000 (-0.008-0.003)	-0.011 (-0.012-0.009)	-0.035 (-0.053-0.018)
	QRISK3	Full	0.034 (0.028-0.040)	0.011 (-0.014-0.058)	-0.001 (-0.003-0.002)	0.036 (0.029-0.044)	0.025 (-0.011-0.101)
		Cases	0.038 (0.032-0.045)	0.012 (-0.012-0.059)	0.000 (0.000-0.000)	0.040 (0.033-0.049)	0.035 (-0.004-0.124)
		Noncases	-0.004 (-0.005 - -0.003)	-0.001 (-0.003-0.001)	-0.001 (-0.003-0.002)	-0.005 (-0.006-0.004)	-0.011 (-0.023-0.003)
Continuous	PCE	Full	0.405 (0.379-0.424)	0.057 (-0.211-0.291)	0.427 (-0.249-0.849)	0.412 (0.388-0.431)	0.366 (0.269-0.463)
		Cases	0.200 (0.182-0.215)	-0.026 (-0.245-0.184)	0.285 (-0.402-0.599)	0.206 (0.186-0.221)	0.175 (0.104-0.257)
		Noncases	0.205 (0.197-0.213)	0.084 (-0.012-0.183)	0.142 (-0.007-0.347)	0.207 (0.195-0.217)	0.191 (0.158-0.233)
	QRISK3	Full	0.395 (0.373-0.418)	0.173 (-0.207-0.673)	0.300 (-0.338-0.780)	0.403 (0.377-0.426)	0.355 (0.232-0.456)
		Cases	0.195 (0.177-0.214)	0.059 (-0.165-0.443)	0.164 (-0.496-0.594)	0.201 (0.183-0.218)	0.173 (0.073-0.246)
		Noncases	0.200 (0.192-0.210)	0.114 (-0.013-0.406)	0.137 (-0.015-0.383)	0.202 (0.193-0.210)	0.183 (0.138-0.243)

The improvement in the predictive performance of the addition of the GPS_{Mult} to the ACC/AHA Pooled Cohort Equations (PCE) or QRISK3 was evaluated in each ancestry using continuous and categorised net reclassification improvement (NRI), with a risk probabilities threshold of 7.5% obtained with Kaplan-Meier estimates for a period of 10 years and confidence intervals (95%) obtained from 100-fold bootstrapping.

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