Supplemental Table 1. Definition of coronary artery disease, cerebrovascular disease, chronic kidney disease and diabetes.

Disease	HES statistics ICD-10	HES statistics ICD-9	HES statistics OPCS-4	Non-cancer illness (20002)	Operation code (20004)	Other data fields
Coronary artery disease, n (%)	I21, I22, I23, I24.1, I25.2	410*, 411*, 412*, 429.79, 413, 414	K40.1-4, K41.1-4, K45.1-5, K49.1-2, K49.8-9, K50.2, K75.1-4, K75.8-9, K40	1074, 1075	1070, 1095	Vascular/heart problems, diagnosed by doctor: Biobank field: 6150, 1: Heart attack
Cerebrovascular disease, n (%)	I63.*, I64.*, G45.*	434.*, 435.*, 436.*	L29.4, L29.5, L30.3, L31.1, L31.3, L31.4, L35.4, L37.2	1082, 1583	1105, 1109	Vascular/heart problems; diagnosed by doctor (Biobank field: 6150, 3:Stroke)
Chronic kidney disease, n (%)	N183, N184, N185	5853, 5855, 5954		1192, 1193		
Type 1 diabetes	E10, O230;	25001, 25011, 25021, 25031, 25041, 25051, 25061, 25093, 25071, 25081, 25091, 25003, 25013, 25023, 25033, 25043, 25053, 25063, 25073, 25083		122,212,231,220		
Type 2 diabetes	E11, O231	25000, 25010, 25020, 25030, 25040, 25050, 25060, 25070, 25080, 25090, 25002, 25012, 25022, 25032, 25042, 25052, 25062, 25072, 25082, 25092				Treatment and medication code, Biobank Field 20003: 1140868902, 1140874646, 1140874674, 1140874718, 1140874744, 1140883066, 1140884600, 1141152590, 1141157284, 1141168660, 1141171646, 1141173882, 1141189090; Biobank field 2443 = 1

Supplemental Table 2. Definition of Peripheral Artery Disease

Field name	Data Code	Data code definition
Non-cancer illness code, self-reported (20002)	1067	Peripheral vascular disease
	1087	Leg claudication/ intermittent claudication
	1088	Arterial embolism
Diagnoses: main ICD10; secondary ICD10; primary/ secondary cause of death ICD10	I70.0	Atherosclerosis of aorta
	I70.00	Atherosclerosis of aorta (without gangrene)
	I70.01	Atherosclerosis of aorta (with gangrene)
	I70.2	Atherosclerosis of arteries of the extremities
	I70.20	Atherosclerosis of arteries of extremities (without gangrene)
	I70.21	Atherosclerosis of arteries of extremities (with gangrene)
	I70.8	Atherosclerosis of other arteries
	I70.80	Atherosclerosis of other arteries (without gangrene)
	I70.9	Generalized and unspecified atherosclerosis
	I70.90	Generalized and unspecified atherosclerosis (without gangrene)
	I73.8	Other specified peripheral vascular diseases
	I73.9	Peripheral vascular disease, unspecified
Diagnoses main ICD9; secondary ICD9	4400	Atherosclerosis of aorta
	4402	Atherosclerosis of arteries of the extremities
	4438	Other specified peripheral vascular disease
	4439	Peripheral vascular disease, unspecified
Operation code, self-reported (20004)	1102	Fem-pop bypass/leg artery bypass
	1108	Leg artery angioplasty +/- stent
	1440	Amputation of leg
	X09.3	Amputation of leg above knee
	X09.4	Amputation of leg through knee
	X09.5	Amputation of leg below knee

Supplemental Table 2. Definition of Peripheral Artery Disease

Field name	Data Code	Data code definition
Operative procedures main OPCS; Operative procedures secondary OPCS	L21.6	Bypass of bifurcation of aorta by anastomosis of aorta to iliac artery NEC
	L51.3	Bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
	L51.6	Bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
	L51.8	Other specified other bypass of iliac artery
	L52.1	Endarterectomy of iliac artery and patch repair of iliac artery
	L52.2	Endarterectomy of iliac artery NEC
	L54.1	Percutaneous transluminal angioplasty of iliac artery
	L54.4	Percutaneous transluminal insertion of stent into iliac artery
	L54.8	Other specified transluminal operations on iliac artery
	L59.1	Bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
	L59.2	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
	L59.3	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
	L59.4	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
	L59.5	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
	L59.6	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
	L59.7	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
	L59.8	Other specified other bypass of femoral artery
	L60.1	Endarterectomy of femoral artery and patch repair of femoral artery
	L60.2	Endarterectomy of femoral artery NEC
	L63.1	Percutaneous transluminal angioplasty of femoral artery
	L63.5	Percutaneous transluminal insertion of stent into femoral artery
	L63.9	Unspecified transluminal operations on femoral artery
	L66.7	Percutaneous transluminal placement of peripheral stent in artery
Medication	1141181150	cilostazol
	1141181154	pletal 100mg tablet

Supplemental Table 3. Comparison of genome-wide polygenic risk scores based on tuning parameters using PRScs

	AUC[a]	95% CI	*P* value
***P* value threshold**			
1	0.716	(0.709, 0.723)	Ref
0.5	0.715	(0.708, 0.722)	0.245
0.4	0.715	(0.708, 0.722)	0.143
0.3	0.715	(0.708, 0.722)	0.046
0.2	0.715	(0.708, 0.722)	0.022
0.1	0.714	(0.707, 0.721)	8.716×10^{-3}
0.05	0.714	(0.707, 0.721)	6.062×10^{-3}
0.001	0.710	(0.703, 0.717)	5.611×10^{-7}
5×10^{-8}	0.706	(0.699, 0.713)	3.748×10^{-13}
Global shrinkage parameter phi (with *P* value threshold = 1)			
1×10^{-4}	0.716	(0.707, 0.723)	Ref
1	0.710	(0.703, 0.717)	8.177×10^{-10}
1×10^{-2}	0.713	(0.706, 0.720)	2.721×10^{-5}
1×10^{-6}	0.712	(0.705, 0.720)	8.793×10^{-5}
Not specified	0.715	(0.706, 0.723)	0.728

Results were rounded off to three decimal places to show the difference in detail. [a]AUC: area under the curve was calculated using logistic regression (adjusted for age, sex, the first 5 PCs) in a validation dataset of 487,320 participants in the UK Biobank of which 5,759 had been diagnosed with PAD. CI: Confidence Interval.

Supplemental Table 4. Area under the curve for PRS based on PAD and CAD GWAS

	PRSice			PRScs		
GWAS data	**AUC[a]**	**95% CI**	***P***	**AUC**	**95% CI**	***P***
MVP PAD	0.707	(0.699, 0.713)	Ref	0.716	(0.709, 0.723)	Ref
C4D CAD	0.705	(0.698, 0.712)	0.150	0.705	(0.698, 0.712)	0.033
CARDIoGRAM	0.706	(0.699, 0.714)	0.906	0.708	(0.700, 0.715)	0.019

Results were rounded off to three decimal places to show the difference in detail. [a]AUC: area under the curve was calculated using logistic regression (adjusted for age, sex, the first 5 PCs) in a validation dataset of 487,320 participants in the UK Biobank of which 5,759 had been diagnosed with PAD. [b]Statistical significance of AUC was calculated by Delong's test. PAD – peripheral artery disease; CAD – coronary artery disease; CI - Confidence Interval; MVP – Million Veterans Program; CARDIoGRAM - Coronary Artery Disease Genome-Wide Replication and Meta-Analysis; C4D - CARDIoGRAM plus The Coronary Artery Disease consortium.

Supplemental Table 5. Performance of a PRS-enhanced Clinical Risk Model for PAD

Group		AUC, mean (min, max)[a]	NRI, 95% CI[b]
Sex	**Men**	0.77 (0.75, 0.78)	0.10 (0.09, 0.11)
	Women	0.69 (0.65, 0.72)	0.04 (0.03, 0.06)
Race	**European**	0.76 (0.75, 0.78)	0.04 (0.03, 0.06)
	Non-European	0.71 (0.67, 0.75)	0.03 (-0.06, 0.13)
Age	**> 50**	0.76 (0.74, 0.78)	0.10 (0.08, 0.11)
	≤ 50	0.63 (0.57, 0.70)	0.05 (0.01, 0.09)
All individuals		0.76 (0.75, 0.77)	0.07 (0.06, 0.08)

[a]AUC, mean (min, max): Mean value (minimum value, maximum value) of area under the curve was calculated by 10-fold cross validation with 454,486 participants in the UK Biobank of which 5,228 had been diagnosed with PAD; [b]NRI: Net reclassification index compared PRS-enhanced clinical risk model with clinical risk model. PAD – peripheral artery disease; NRI – net reclassification index.

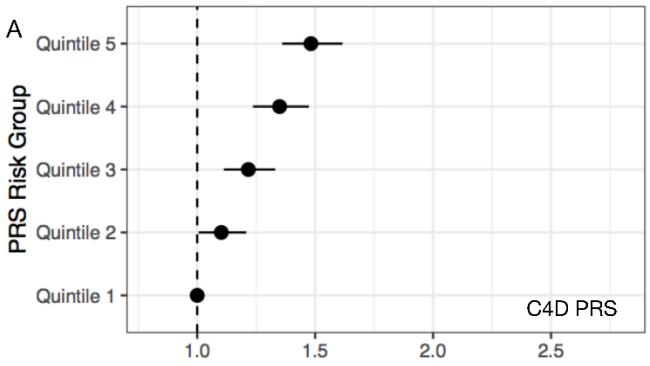
Supplemental Table 6. Reclassification Table for PRS-enhanced Clinical Risk Model

		PRS-enhanced model				
Group	**Clinical model**	**0 - 0.5%**[a]	**0.5-1%**	**1-2%**	**> 2%**	**% Reclassified**
Controls	**0 - 0.5%**	123272	13617	544	4	10
	0.5-1%	30850	105636	12887	338	29
	1-2%	753	29614	76214	9066	34
	> 2%	0	126	5255	46310	10
Cases	**0 - 0.5%**	476	74	12	0	15
	0.5-1%	123	554	121	7	31
	1-2%	3	232	1034	269	33
	> 2%	0	2	91	2230	4
All	**0 - 0.5%**	122796	13543	532	4	10
	0.5-1%	30727	105082	12766	331	29
	1-2%	750	29382	75180	8797	34
	> 2%	0	124	5164	44080	11

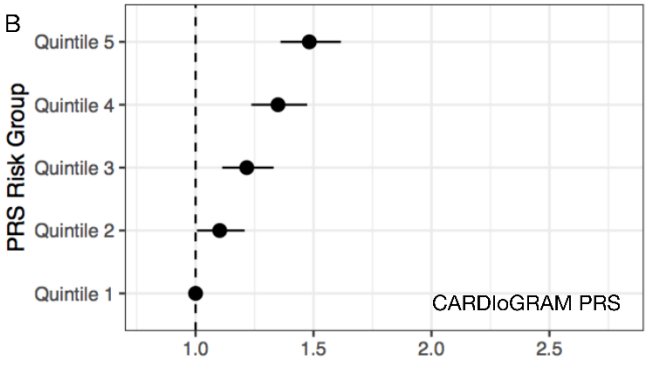
[a]The prevalence of PAD in UK Biobank is 1%. Cutoff thresholds were set at 0.5%, 1%, 2% and > 2%.

Supplemental Figure Legend

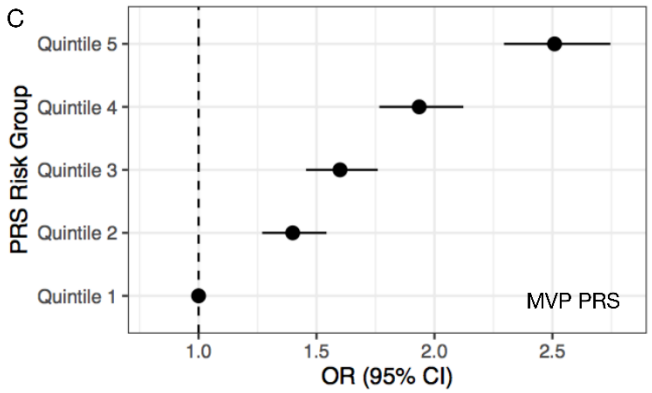
Supplemental Figure 1. Disease risk estimated from polygenic risk score (PRS) derived from different genome-wide association studies (GWAS). (A-C) Peripheral artery disease (PAD) risk estimated from PRS calculated with C4D, CARDIoGRAM and the PAD-specific Million Veterans Program GWAS, respectively. OR: Odds ratio. Estimates were derived by conditional logistic regression adjusting for age, sex, and the first 5 principal components.



PRS Quintile	OR (95% CI)	P value
Quintile 5	1.48 (1.36, 1.62)	3.38×10^{-19}
Quintile 4	1.35 (1.24, 1.47)	2.00×10^{-11}
Quintile 3	1.22 (1.11, 1.33)	1.69×10^{-5}
Quintile 2	1.10 (1.01, 1.21)	3.71×10^{-2}
Quintile 1	Ref.	Ref.

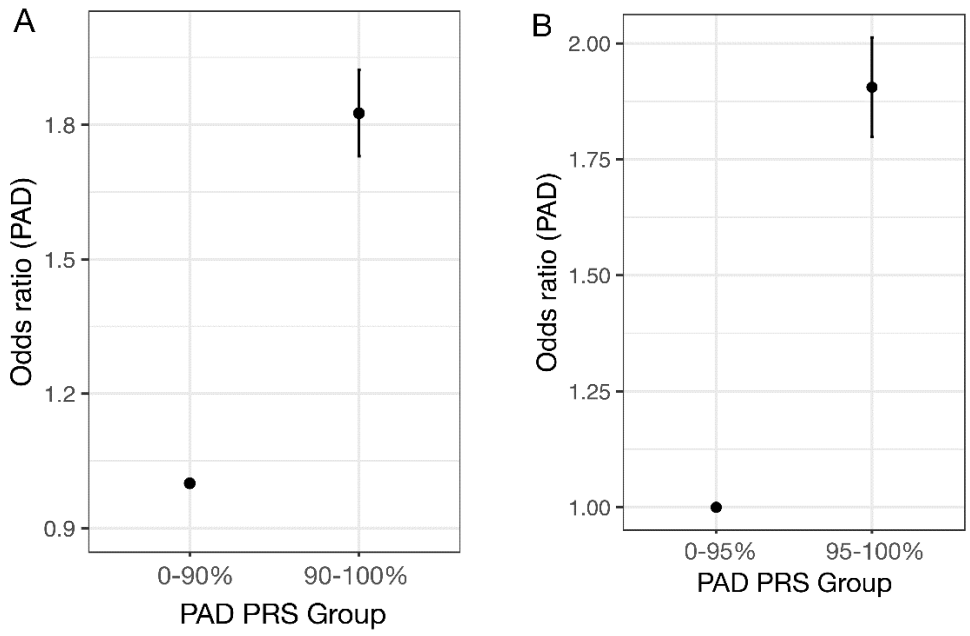


PRS Quintile	OR (95% CI)	P value
Quintile 5	1.65 (1.51, 1.79)	1.45×10^{-30}
Quintile 4	1.32 (1.21, 1.44)	7.51×10^{-10}
Quintile 3	1.25 (1.14, 1.37)	1.00×10^{-6}
Quintile 2	1.10 (1.00, 1.20)	5.52×10^{-2}
Quintile 1	Ref.	Ref.

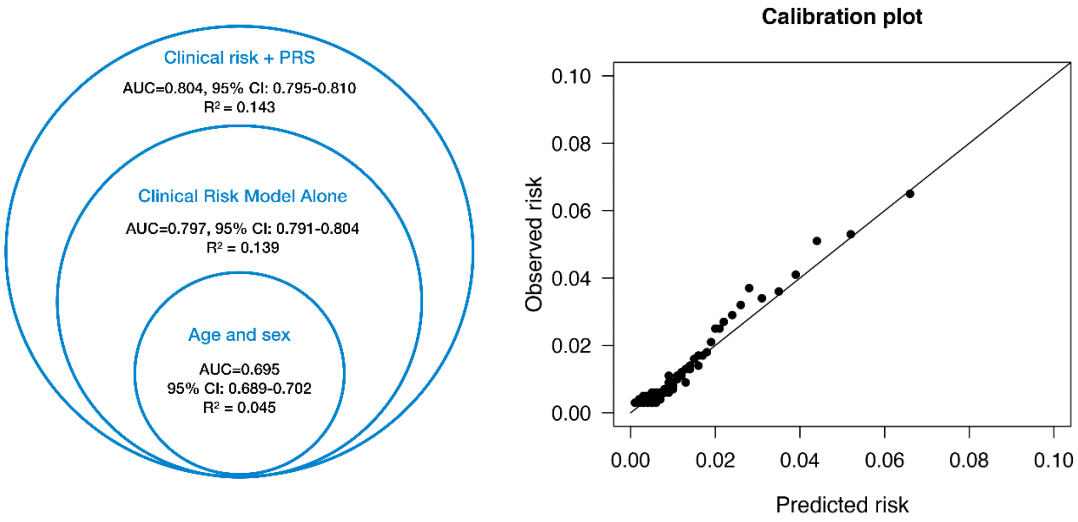


PRS Quintile	OR (95% CI)	P value
Quintile 5	2.51 (2.29, 2.75)	1.04×10^{-89}
Quintile 4	1.94 (1.77, 2.12)	4.10×10^{-45}
Quintile 3	1.60 (1.46, 1.76)	2.81×10^{-22}
Quintile 2	1.40 (1.27, 1.54)	1.31×10^{-11}
Quintile 1	Ref.	Ref.

Supplemental Figure 2. Genome-wide polygenic risk score (PRS) and the risk of peripheral artery disease (PAD). (A-B) Odds of PAD in the UK biobank population for those with PRSs in the top 10th (A) and 5th percentiles (B) compared to the rest of the population.



Supplemental Figure 3. Goodness of fit and calibration metrics. (A) Goodness of fit. With increasing model complexity, the model goodness-of-fit increases, as does the R^2. The addition of the genome-wide polygenic risk score (PRS) provides additional discrimination ability compared to a clinical model alone. **(B)** Calibration curve. Visual inspection of the calibration curve demonstrates that on average the predicted cohort risk in the PRS-enhanced model is similar to the observed risk.



Supplemental Figure 4. The prevalence of peripheral artery disease (PAD) in deciles of clinical risk score and polygenic risk score (PRS)-enhanced score. A clinical risk score and PRS-enhanced score were calculated and categorized into deciles. The prevalence of PAD is shown based on each decile.