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Polygenic Prediction of Peripheral Artery Disease and Major Adverse Limb Events

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IMPORTANCE Peripheral artery disease (PAD) is a heritable atherosclerotic condition associated with functional decline and high risk for limb loss. With growing knowledge of the genetic basis for PAD and related risk factors, there is potential opportunity to identify individuals at high risk using polygenic risk scores (PRSs).

OBJECTIVE To develop a novel integrated, multiancestry polygenic score for PAD (PRS-PAD) and evaluate its risk estimation for PAD and major adverse limb events in 3 populations.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal cohort study was conducted among individuals with genotyping and electronic health record data in the UK Biobank (2006-2021), All of Us (AoU, 2018-2022), and the Mass General Brigham Biobank (MGBB, 2010-2023). Data were analyzed from July 2023 to February 2025.

EXPOSURES PRS-PAD, previously published PAD polygenic scores, and clinical risk factors.

MAIN OUTCOMES AND MEASURES The primary outcomes were PAD and major adverse limb events, defined as a surrogate of major amputation and acute limb ischemia.

RESULTS The study populations included 400 533 individuals from the UK Biobank (median [IQR] age, 58.2 [45.0-71.4] years; 216 215 female participants [53.9%]), 218 500 from AoU (median [IQR] age, 53.6 [37.7-65.0] years; 132 647 female participants [60.7%]), and 32 982 from MGBB (median [IQR] age, 56.0 [32.0-80.0] years; 18 277 female participants [55.4%]). In the UK Biobank validation cohort, PRS-PAD was associated with an odds ratio [OR] per SD increase of 1.63 (95% CI, 1.60-1.68; $P < .001$). After adjusting for clinical risk factors, the OR for the top 20% of PRS-PAD was 1.68 (95% CI, 1.62-1.74; $P < .001$) compared to the remainder of the population. Among PAD cases without a history of diabetes, smoking, or chronic kidney disease (n = 3645), 1097 individuals (30.1%) had a high PRS-PAD (top 20%). In incident disease analysis, PRS-PAD improved discrimination (C statistic, 0.761), which was nearly equivalent to the performances of diabetes (C statistic, 0.760) and smoking (C statistic, 0.765). Among individuals with prevalent PAD, high PRS-PAD was associated with an increased risk of incident major adverse limb events in the UK Biobank (hazard ratio [HR], 1.75; 95% CI, 1.18-2.57; $P = .005$), MGBB (HR, 1.56; 95% CI, 1.06-2.30; $P = .02$), and AoU (HR, 1.57; 95% CI, 1.06-2.33; $P = .03$).

CONCLUSIONS AND RELEVANCE This cohort study develops a new PRS that stratifies risk of PAD and adverse limb outcomes. Incorporating polygenic risk into PAD care warrants further investigation to guide screening and tailor management to prevent major adverse limb events.

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Supplemental content

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Peripheral artery disease (PAD) affects a global population of 230 million adults, with high resource utilization owing to both systemic and limb ischemic events.[1,2] While PAD shares risk factors with coronary artery disease (CAD), 32% to 54% of individuals presenting with PAD do not have clinically significant coronary or cerebrovascular disease.[3,4] In addition, genome-wide association studies (GWAS) have revealed distinct mechanisms underlying PAD and other atherosclerotic conditions.[5]

Despite being an underdiagnosed condition with high morbidity and cardiovascular mortality, there is a lack of consensus on screening for PAD from American and European guidelines.[6-8] In addition, there is no standard tool to predict complications before advanced disease develops.[7]

Polygenic risk scores (PRSs) provide a single metric for the inherited component of disease risk by integrating variants discovered from GWAS. While there have been advances in PRS to optimize risk stratification for a number of cardiovascular diseases, there has been limited progress in developments for PAD owing to largely European-based data and unclear transferability.[9-11] Additionally, PRS utility for incident prediction of adverse PAD events has not been described.

To address these needs, we developed a new genome-wide polygenic score for PAD (PRS-PAD) that incorporates multiancestry GWAS data for PAD and related traits from more than 2 million individuals (eFigure 1 in Supplement 1). We assessed the performance of PRS-PAD in predicting PAD in a 304 294-individual internal validation cohort and 2 independent study populations composed of 251 492 individuals. Lastly, we applied PRS-PAD to identify individuals with clinically important increased risk for major adverse limb events.

Key Points

Question How does a polygenic risk score (PRS) perform in estimation of peripheral artery disease (PAD) and major adverse limb events?

Findings In this cohort study of 3 populations, a new PRS was significantly associated with PAD and stratified risk for incident major adverse limb events. Addition of high PRS (top 20%) to guideline-recommended screening criteria increased the proportion of identified cases of incident PAD.

Meaning Polygenic background shows potential utility in primary and secondary prevention of PAD; however, further research is needed to optimize performance in non-European populations and determine its associated effect on vascular outcomes.

Methods

Study Design and Populations

PRS-PAD was fine-tuned in the UK Biobank using the largest single-ancestry sample as a training set (n = 96 239 European individuals).[12] The score was validated in multiancestry cohorts, including an independent UK Biobank dataset (n = 304 294; data from 2006-2021), the Mass General Brigham Biobank (MGBB; n = 32 892; data from 2010-2023),[13] and All of Us (AoU; n = 218 500; data from 2018-2022).[14] Descriptions of the study populations, phenotyping, and genotyping can be found in the eMethods and in eTables 2 and 3 in Supplement 1 and in eTable 1 in Supplement 2. All participants provided written informed consent. The institutional review board at Massachusetts General Hospital approved study protocols. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Clinical End Points

In the UK Biobank and AoU, PAD was defined based on electronic health record (EHR) diagnosis, procedure codes for lower extremity revascularization or major amputation, and self-reported history (eTables 4 and 5 in Supplement 2).[15] In the MGBB, a complementary phenotyping approach was used to phenotype PAD based on both codes and unstructured EHR data (eg, clinical notes or reports). The MGBB has curated these validated phenotypes to leverage the granular data from consenting patients throughout the Mass General Brigham health system using phenotyping algorithms that extract relevant features from an enterprise EHR data warehouse for patient identification in research studies (eMethods in Supplement 1).[16] Minimum ankle-brachial index (ABI) values were extracted from imaging reports from the EHR.

Major adverse limb events were defined as major amputation or acute limb ischemia using diagnosis and procedure codes (eTables 6-8 in Supplement 2). Revascularization included thrombectomy, thrombolysis, and emergency lower extremity bypass.

PRS-PAD Construction

To leverage the common mechanistic pathways of PAD and related traits, GWAS results of PAD and 14 other atherosclerotic traits or risk factors were considered in PRS-PAD construction: PAD, CAD, ischemic stroke, glomerular filtration rate, diabetes, smoking, systolic blood pressure (SBP), diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index (BMI), carotid plaque burden, and carotid intima-media thickness (eTable 9 in Supplement 2).

PRS-PAD was developed in a 2-layer process (eFigure 1 in Supplement 1).[17] Layer 1 involved using ancestry-stratified, trait-specific GWAS data to calculate multiancestry polygenic scores that were optimized according to their PAD predictive performance. Scores were calculated using LDpred2, a Bayesian method that adjusts marginal effect sizes for population-specific linkage disequilibrium patterns (R package bigsnpr version 11.4 [R Foundation]),[18] yielding 100 scores across all ancestries and traits. The ancestry-specific scores were combined into the best-performing multiancestry score using least absolute shrinkage and selection operator (LASSO) regression models predicting PAD (R package glmnet versions 4.0-2 [R Foundation]). Feature selection was performed iteratively for 15 traits, yielding 15 multiancestry, trait-specific scores (eTable 9 in Supplement 2).

In layer 2, scores from layer 1 were input into a LASSO regression model predicting PAD to construct the final integrated and multitrait PRS-PAD. Of the 15 candidate scores, 11

traits contributed to PRS-PAD (eTable 10 in Supplement 2). The final PRS-PAD was then calculated in the validation datasets. Details on PRS-PAD construction are available in the eMethods in Supplement 1.

PRS-PAD Validation and Benchmarking

PRS-PAD performance was compared with previously published PRSs in the Polygenic Score Catalog.[19] PRS-penalized logistic regression (PLR) (Polygenic Score Catalog identifier: PGS001843) is a single-trait score for PAD developed using LASSO regression and individual-level European data from the UK Biobank.[10] PRS-LDpred2 (catalog identifier: PGS002055) is another single-trait score calculated with LDpred2-auto based on UK Biobank summary statistics.[10] For comparison to an existing clinical score, we calculated the lifetime PAD risk score in individuals in the UK Biobank (eMethods in Supplement 1).[20,21]

Statistical Analysis

The unadjusted rate of PAD was calculated across percentiles of PRS-PAD. Model calibration was assessed with the Hosmer-Lemeshow test (R ResourceSelection versions 0.3-6 [R Foundation]) and by comparing the observed and predicted prevalence across percentiles calculated using a logistic regression model with only PRS-PAD as a predictor.

The associations of PRS-PAD and other scores with all PAD (incident and prevalent cases) were assessed using logistic regression. We evaluated PRSs as a continuous PRS (OR/SD) and in genetic risk categories of varying extremes of polygenic score percentiles (OR). Variance explained was determined using Nagelkerke R^2 (R package fmsb version 0.7.5 [R Foundation]). Incident event analyses were performed using Cox proportional hazards models with metrics including hazard ratios (HRs) and C statistics (R survival versions 3.5-7 [R Foundation]). Adverse limb event analyses were restricted to individuals with prevalent PAD. Time to major adverse limb event curves were estimated using the Kaplan-Meier method, standardized to mean age and sex (R survminer version 0.4.9 [R Foundation]). Linear regression was used to evaluate the relationship between polygenic scores and minimum ABI.

Logistic, linear, and Cox models including polygenic scores were adjusted for age, sex, genotyping array, and the first 10 principal components (PCs). In the UK Biobank, we tested the strength of PRS-PAD associations with PAD and incident major adverse limb events after additionally accounting for current smoking, hypertension, diabetes, hyperlipidemia, and chronic kidney disease.

To assess the additional value of PRS-PAD in detecting incident PAD, we calculated event rates based on guideline-recommended screening criteria (see the eMethods in Supplement 1 and eTable 11 in Supplement 2)[7] and in combination with high PRS-PAD (defined as top 20% or top 10%). Cox regression was used to calculate 10-year event rates, standardized to the mean of covariates in each population.

PRS-PAD and other continuous variables were scaled to a mean of zero and 1 SD. Statistical significance was defined as $P < .05$, with 2-tailed tests, or 95% confidence intervals that excluded the null value. Statistical analyses were performed using R version 4.1.0 (R Foundation).

Results

Given that complex diseases like PAD share genetic backgrounds with related traits, we leveraged this genetic correlation to more fully capture human genetic architecture and to construct PRS-PAD.[5,22,23] PRS-PAD integrated 1 296 243 variants across 5 ancestries and 11 traits, including PAD, smoking, CAD, ischemic stroke, diabetes, SBP, LDL-C, glomerular filtration rate, BMI, carotid intima-media thickness, and total cholesterol. PRS-PAD was predominantly derived from European discovery data (73%, eTable 10 in Supplement 2). Of the non-European populations, African GWAS discovery data contributed the most to PRS-PAD (9.6%), followed by summary statistics from Latino (8.6%), East Asian (6.1%), and South Asian (2.6%) populations.

Population Characteristics

The study populations included 400 533 individuals from the UK Biobank (median [IQR] age, 58.2 [45.0-71.4] years; 216 215 female participants [53.9%]), 218 500 from AoU (median [IQR] age, 53.6 [37.7-65.0] years; 132 647 female participants [60.7%]), and 32 982 from MGBB (median [IQR] age, 56.0 [32.0-80.0] years; 18 277 female participants [55.4%]). PRS-PAD was validated in a holdout UK Biobank cohort including 304 294 individuals of diverse ancestries (164 108 female participants [53.9%]; 2.3% African, 0.6% East Asian; 94% European, 0.51% Middle Eastern and North African, and 2.5% South Asian individuals). The AoU validation cohort was composed of 218 500 individuals (132 647 female participants [60.7%]; 23.7% African, 2.4% East Asian, 55% European, 18% Latino, 0.2% Middle Eastern and North African, and 1.0% South Asian individuals). The MGBB testing set included 32 982 individuals (18 277 female participants [55.4%]; 5.4% African, 87% European, and 7.7% Latino individuals). Clinical characteristics of the study populations are outlined in **Table 1**.

Association of PRS-PAD With PAD Risk

Within the UK Biobank, PRS-PAD was associated with an OR per SD of 1.77 (95% CI, 1.70-1.86) for PAD and an R^2 of 0.10 in the European training sample (eTable 12 in Supplement 1). The effect size in the multiancestry UK Biobank validation cohort was OR per SD of 1.63 (95% CI, 1.60-1.68), with an R^2 value of 0.087. After accounting for hypertension, hyperlipidemia, current smoking, diabetes, and chronic kidney disease, the continuous PRS-PAD had an adjusted OR per SD of 1.32 (95% CI, 1.29-1.36). Those in the top 20% of PRS-PAD had an adjusted OR of 1.68 (95% CI, 1.62-1.74) compared to the remainder of the population. Among PAD cases without a history of diabetes, smoking, or chronic kidney disease (n = 3645), 1097 individuals (30.1%) had a high PRS-PAD (top 20%).

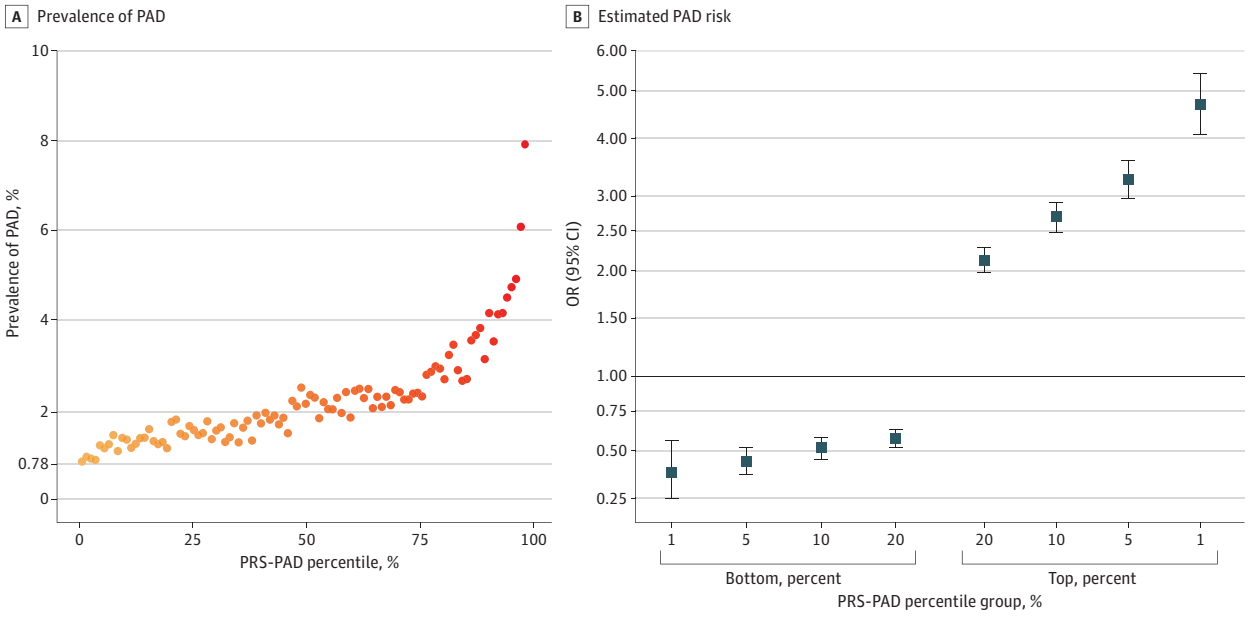
We found significant differences in PAD rates across the PRS-PAD percentile distribution, ranging from 0.78% to 7.91% (**Figure 1**A). Predicted PAD prevalence was overall consistent with observed prevalence, excluding the 98% and higher percentile where there was slight risk underestimation by PRS-PAD alone driven by a sharp increase in observed PAD prevalence (eFigure 2 in Supplement 1). The top 1% of PRS-PAD had

Table 1. Baseline Characteristics of the Training and Validation Cohorts

Characteristic	No. (%)			
	UK Biobank			
	Training	Validation	MGB Biobank	All of Us
Participants, No.	96 239	304 294	32 982	218 500
Total PAD cases	2086 (2.2)	6564 (2.2)	1027 (3.11)	12 467 (5.7)
Age, median (IQR), y	58.6 (45.6-71.6)	58.2 (45.1-71.3)	56.0 (32.0-80.0)	53.6 (37.7-65.0)
Sex				
Female	52 107 (54.1)	164 108 (53.9)	18 277 (55.4)	132 647 (60.7)
Male	44 132 (45.9)	140 186 (46.1)	14 705 (44.6)	85 853 (39.3)
Ancestry				
African	NA	6939 (2.3)	1778 (5.4)	51 691 (23.7)
East Asian	NA	1761 (0.58)	NA	5268 (2.4)
European	96 239 (100)	286 356 (94.1)	28 656 (86.9)	119 167 (54.5)
Latino	NA	NA	2548 (7.7)	39 576 (18.1)
Middle Eastern	NA	1558 (0.51)	NA	509 (0.2)
South Asian	NA	7680 (2.52)	NA	2289 (1.0)
Chronic kidney disease	324 (0.34)	1064 (0.35)	2939 (8.9)	10 708 (4.9)
Current smoker	9967 (10.3)	31 365 (10.3)	938 (2.8)	55 325 (25.3)
Hyperlipidemia	18 780 (19.5)	59 498 (19.6)	13 844 (41.9)	69 282 (31.7)
Hypertension	26 851 (27.9)	86 695 (28.5)	15 805 (47.9)	81 040 (37.1)
Diabetes	4804 (4.99)	16 929 (5.56)	3559 (10.8)	27 807 (12.7)
History of CAD	3313 (3.44)	10 578 (3.48)	2963 (8.9)	14 195 (6.5)
Statin use	15 428 (16.0)	49 788 (16.4)	10 168 (30.8)	41 371 (18.9)

Abbreviations: CAD, coronary artery disease; MGB, Mass General Brigham; NA, not applicable; PAD, peripheral artery disease.

Figure 1. Polygenic Prediction of Peripheral Artery Disease (PAD) in the UK Biobank



A, Prevalence of PAD across polygenic risk score (PRS)-PAD percentiles in the UK Biobank validation dataset (n = 304 294). B, Estimated PAD risk in the top and bottom of PRS-PAD percentile distributions relative to the middle quintile (40%-59%) of the UK Biobank testing dataset. Results are shown on a log axis. Error bars represent 95% confidence intervals of the odds ratios (ORs).

a 4.71-fold increased PAD risk (OR, 4.71; 95% CI, 4.07-5.42), and the bottom 1% had a 0.38-fold decreased odds for PAD (OR, 0.38; 95% CI, 0.25-0.56) compared to the middle quintile (Figure 1B).

Across ancestries, PRS-PAD was associated with PAD in African, East Asian, European, Middle Eastern and North African, and South Asian subgroups (**Table 2**). While PRS-LDpred2 and PRS-PLR estimated PAD risk in European

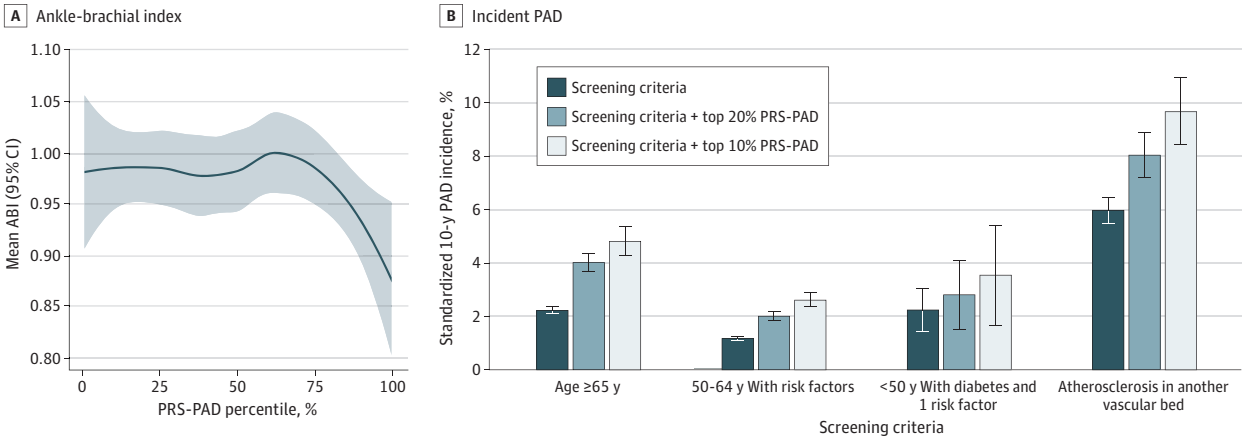
Table 2. Risk of Peripheral Artery Disease (PAD) Associated With Polygenic Risk Score (PRS)-PAD in Ancestry Subgroups in the UK Biobank Validation Cohort[a]

Ancestry	PAD, No./total No. (%)	OR/SD (95% CI)	*P* value
African	126/6939 (1.8)	1.26 (1.01-1.59)	.04
East Asian	20/1761 (1.1)	1.60 (1.01-2.53)	.04
European	6205/286 356 (2.2)	1.66 (1.62-1.71)	<.001
Middle Eastern or North African	30/1558 (1.9)	1.62 (1.10-2.44)	.02
South Asian	183/7680 (2.4)	1.25 (1.07-1.46)	.004

Abbreviation: OR/SD, odds ratio per standard deviation change in PRS-PAD.

[a] Results were calculated from a logistic regression model with age, sex, genotyping array, and 10 principal components as covariates.

Figure 2. Polygenic Risk Score–Peripheral Artery Disease (PRS-PAD) Associates With Ankle-Brachial Index (ABI) Measurements and Identifies More Incident Cases of PAD



A, Loess regression plot of PRS-PAD and minimum ABI among a subset of individuals in the Mass General Brigham Biobank (n = 763). The mean ABI in each percentile group is shown, with shaded area representing 95% confidence intervals. B, 10-Year incidence of first-occurring PAD events from prospective analyses of individuals without prior PAD in the UK Biobank. Cox proportional hazards regression models were used to calculate the 10-year event rates based on criteria that current clinical guidelines recommend ABI screening[7] and in combination with high genetic risk (top 20% or top 10% of PRS-PAD). Error bars represent 95% confidence intervals of event rates.

individuals, both were not associated with PAD in non-European subgroups (eTable 13 in Supplement 2). In clinical subgroups, PRS-PAD performance was fairly stable, with ORs per SD between 1.33 and 1.72 (eFigure 3 in Supplement 1).

Validation of PRS-PAD in Distinct External Cohorts

In the MGBB, there were greater odds of PAD with increased PRS-PAD (OR/SD, 1.26; 95% CI, 1.18-1.37). PRS-PAD similarly estimated PAD in AoU (OR/SD, 1.21; 95% CI, 1.19-1.23).

When considering genetic risk categories, PRS-PAD improved risk stratification in external cohorts relative to prior PRSs. In AoU, the highest 20% PRS-PAD had an OR of 1.71 (95% CI, 1.61-1.81) and the middle quintile had an OR of 1.31 (95% CI, 1.23-1.39) relative to the bottom 20% (eFigure 4 in Supplement 1). In the MGBB, high PRS-PAD was associated with an 86% greater odds of PAD (OR, 1.86; 95% CI, 1.51-2.27) relative to the bottom quintile (eFigure 4 in Supplement 1). In both external cohorts, effect estimates were weaker or not significant when comparing genetic risk groups according to PRS-LDpred2 and PRS-PLR.

PRS-PAD demonstrated improved portability across ancestry-based subgroups. Among African (n = 51 691), European (n = 119 167), Latino (n = 39 576), and South Asian (n = 2289) populations in AoU, high PRS-PAD was the most strongly associated with disease compared to prior PRSs (eFigure 4 in Supplement 1 and eTable 14 in Supplement 2). In AoU, high PRS-PAD was associated with an OR of 1.29 (95% CI, 1.27-1.49) among participants of African ancestry, an OR of 1.90 (95% CI, 1.76-2.04) among those of European ancestry, an OR of 1.62 (95% CI, 1.38-1.90) among those of Latino ancestry, and an OR of 3.10 (OR, 3.10; 95% CI, 1.14-8.41) among those of South Asian ancestry. No scores were associated with PAD among East Asian and Middle Eastern and North African populations in AoU (eTables 13 and 14 in Supplement 2).

In the MGBB, PRS-PAD was transferable to European populations (n = 28 656; eFigure 4 in Supplement 1) but did not stratify PAD risk in non-European subgroups (eFigure 4 in Supplement 1 and eTables 13 and 14 in Supplement 2).

Association of PRS-PAD With ABIs

In addition to predicting binary PAD presence, we evaluated whether PRS-PAD was associated with reduced ABI in the MGBB (n = 883; eFigure 5 in Supplement 1). ABIs for PAD cases and controls are shown in eFigure 6 in Supplement 1. PRS-PAD was significantly associated with a −0.088 reduction in ABI for each 1-unit increase in SD of the polygenic score (95% CI, −0.161 to −0.015; **Figure 2**A), while previously published scores were not associated with lower ABI (PRS-PLR: −0.058

change in ABI/SD; 95% CI, −0.127 to 0.011; *P* = .10; PRS-LDpred2: 0.014 change in ABI/SD; 95% CI, −0.059 to 0.087; *P* = .71; eTable 15 in Supplement 1). Those in the top 8% of PRS-PAD had a mean ABI of 0.90 or lower diagnostic of PAD (95% CI, 0.83-0.97) (eFigure 7 in Supplement 1).[24]

Discrimination of Incident PAD According to Polygenic Risk and Clinical Risk Factors

Over a median (IQR) follow-up period of 12.1 (10.6-13.5) years, incident PAD was observed in 4202 individuals in the UK Biobank (1.39%). Among individuals without prior PAD, PRS-PAD was associated an HR per SD of 1.66 (95% CI, 1.61-1.71). The baseline model of age, sex, and PCs had a C statistic of 0.731 (eTable 16 in Supplement 1). The addition of PRS-PAD resulted in a C statistic of 0.761 (ΔC statistic, 0.030), which was approximately equivalent to the additive benefit of diabetes (C statistic, 0.760; ΔC statistic, 0.029) and smoking (C statistic, 0.765; ΔC statistic, 0.034). The C statistic associated with the lifetime PAD risk score was 0.675.[20] The greatest C statistic was observed in a model combining clinical risk factors and PRS-PAD (C statistic, 0.0823; ΔC statistic, 0.092), although the additional improvement of PRS-PAD relative to all risk factors was mild (C statistic, 0.0818; ΔC statistic, 0.087).

Integration of Polygenic Risk With Clinical Guidelines

We then assessed whether PRS-PAD could add incremental value when targeted to high-risk individuals that guidelines recommended screening for PAD.[7] We quantified the 10-year incidence of PAD among individuals who were candidates for ABI screening according to the following criteria from the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines: aged 65 years or older; aged 50 to 64 years with at least 1 atherosclerosis risk factor; younger than 50 years with diabetes and 1 additional risk factor; and known atherosclerosis in another vascular bed.[7] Integrating high PRS-PAD to each screening criteria led to an increase in the proportion of identified incident cases (Figure 2B). For example, among individuals aged 50 to 64 years with at least 1 risk factor, the standardized 10-year PAD incidence increased from 1.14% to 2.58% when integrating the top 10% of PRS-PAD, representing a 2.26-fold increase in identified cases. In addition, among patients with diabetes younger than 50 years with 1 additional risk factor, the addition of top 10% PRS-PAD identified 1.59-fold more cases, from 2.22% to 3.52% (eTable 17 in Supplement 1).

Influence of Preventive Care on Incident PAD in Individuals at High Genetic Risk

Given that high PRS-PAD helped identify more incident cases, we next examined the influence of statin therapy, smoking, and antithrombotic use on PAD incidence in the top 20% PRS-PAD group to explore the potential effect on primary prevention in this high-risk group. Among individuals free of PAD at baseline with high genetic risk (top 20% PRS-PAD [n = 60 387]), nonsmoking status was associated with a 67% lower relative risk of incident PAD compared to active smokers (HR, 0.33; 95% CI, 0.30-0.37), which corresponded to a standardized 10-year incidence of 1.06% among nonsmokers and 3.17% among active smokers. Compared to individuals at high genetic risk who were not receiving statins at baseline, statin therapy was associated with a 2.55-fold greater incident PAD risk (95% CI, 2.31-2.80). Similarly, antithrombotic therapy was associated with an increased risk of incident PAD (HR, 2.85; 95% CI, 2.57-3.13) compared to individuals with no antithrombotic use (eTable 18 in Supplement 1).

Estimating Major Adverse Limb Events Based on Polygenic Risk

Lastly, we assessed whether polygenic background could identify individuals at increased risk for major adverse limb events after PAD diagnosis. In the UK Biobank, individuals with high PRS-PAD (top 20%) had an HR of 1.75 for incident major adverse limb events (95% CI, 1.18-2.57; *P* = .005) over a median (IQR) period of 12.9 (11.7-14.1) years compared to the remainder of individuals with PAD. Those in the top 20% of PRS-PAD were also at greater risk of major adverse limb events in the MGBB (HR, 1.56; 95% CI, 1.06-2.30; *P* = .02) during a median (IQR) duration of 5.19 (2.63-7.75) years of follow-up, as well as in the AoU cohort (HR, 1.57; 95% CI, 1.06-2.33; *P* = .02) over a median (IQR) period of 2.32 (0.35-4.29) years of follow-up (**Figure 3**A).

In the overall PAD cohort in the UK Biobank, PRS-PAD estimated a significant risk gradient for major adverse limb events with a 48% increased relative risk per SD (HR/SD, 1.48; 95% CI, 1.24-1.77; Figure 3B), which remained associated after multivariable adjustment (HR/SD, 1.30; 95% CI, 1.07-1.59). There were consistent associations of PRS-PAD with incident adverse limb events in the PAD cohorts of the MGBB (HR/SD, 1.34; 95% CI, 1.12-1.60) and AoU (HR/SD, 1.33; 95% CI, 1.11-1.58), while other scores demonstrated weaker or nonsignificant risk estimates.

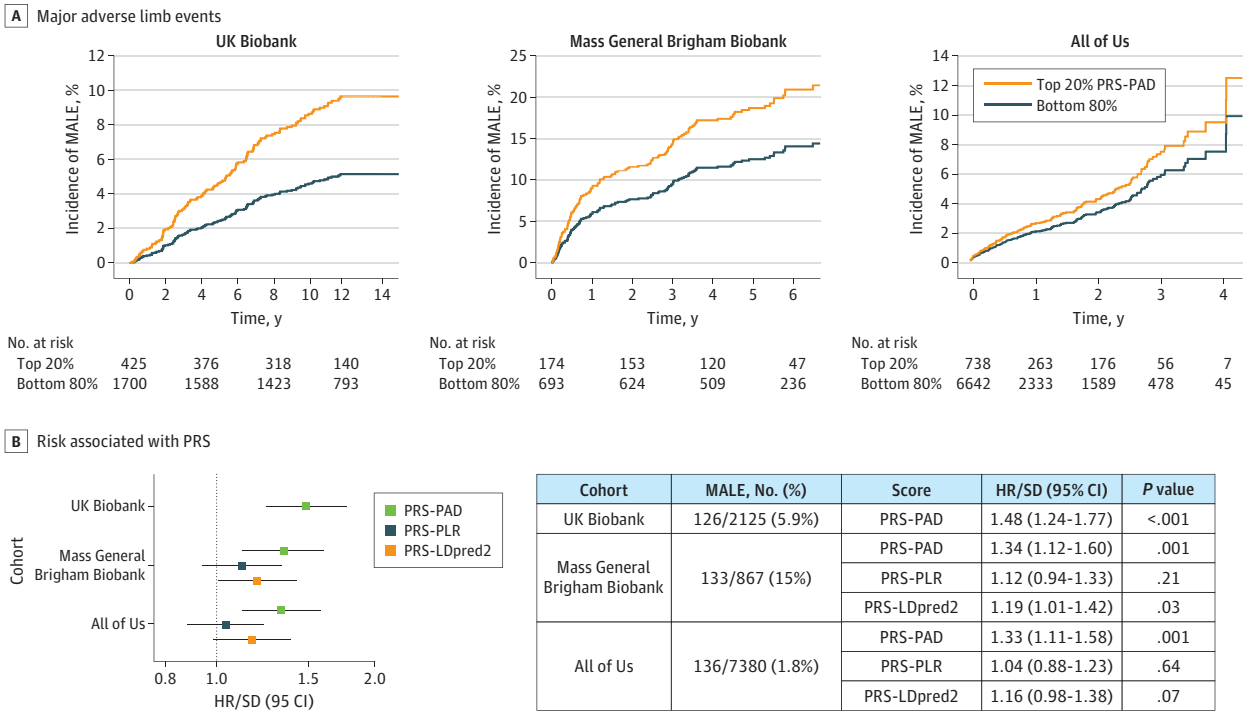
Discussion

In this study, we developed a new polygenic score that aggregates the effects of variants in PAD and related traits across 5 ancestries. This new score shows stronger disease estimation than prior polygenic scores and improved transferability, although the gap between performance in European and non-European groups remains. In addition, PRS-PAD stratifies future major adverse limb events risk in 3 distinct populations with diagnosed PAD.

PRS-PAD builds on prior PAD PRS efforts by newly incorporating multiancestry and multitrait GWAS data in score construction and validating in diverse external cohorts.[9-11] Our framework considered variants discovered from more than 2 million individuals and leveraged the pleiotropy between PAD and related traits to enhance risk estimation.[17,25,26] In addition to stronger disease estimation in European populations in external validation cohorts, PRS-PAD was able to stratify PAD risk in Latino individuals in AoU and both African and South Asian individuals in 2 distinct cohorts (AoU and the UK Biobank). However, the strength of risk associations were comparably mild in individuals of African and Latino ancestries.

In prospective analysis in the UK Biobank, inclusion of PRS-PAD resulted in a comparable benefit in discriminative

Figure 3. Polygenic Risk Score–Peripheral Artery Disease (PRS-PAD) Stratifies Risk for Incident Major Adverse Limb Events (MALE) Among Individuals With PAD



Cohort	MALE, No. (%)	Score	HR/SD (95% CI)	*P* value
UK Biobank	126/2125 (5.9%)	PRS-PAD	1.48 (1.24-1.77)	<.001
Mass General Brigham Biobank	133/867 (15%)	PRS-PAD	1.34 (1.12-1.60)	.001
		PRS-PLR	1.12 (0.94-1.33)	.21
		PRS-LDpred2	1.19 (1.01-1.42)	.03
All of Us	136/7380 (1.8%)	PRS-PAD	1.33 (1.11-1.58)	.001
		PRS-PLR	1.04 (0.88-1.23)	.64
		PRS-LDpred2	1.16 (0.98-1.38)	.07

A, Kaplan-Meier curves of MALE according to high PRS-PAD (top 20%) compared to the remainder of the PAD population, standardized to the mean age and sex of each cohort. B, Risk associated with polygenic scores for incident MALE among individuals with diagnosed PAD in the UK Biobank (n = 2125), Mass General Brigham Biobank (n = 867), and All of Us (n = 7380). Hazard ratios (HRs) were calculated from adjusted Cox regression models including age, sex, genotyping array, and the first 10 principal components of ancestry as covariates. Error bars represent the 95% confidence intervals of the HRs.

capacity as those afforded by smoking and diabetes.[20] Similar to prior studies,[27,28] the addition of a polygenic score to a model already including powerful predictors had modest value in discrimination in the broad population, as evident by the small improvement in C statistics with the addition of PRS-PAD to all traditional risk factors.

PRS-PAD demonstrates the potential to augment risk stratification and targeted screening for PAD. Current American Cardiovascular Society guidelines recommend screening for PAD with ABI in 4 groups: individuals 65 years or older; individuals 50 to 64 years old with atherosclerotic risk factors; individuals younger than 50 years with diabetes and 1 risk factor; and individuals with history of atherosclerosis in other vascular beds.[7,8] When incorporated with screening criteria, addition of high polygenic risk identified more individuals who went on to develop PAD by 1.25- to 1.81-fold when considering the top 20% and 1.59- to 2.26-fold when considering the top 10%. The 2018 US Preventive Services Task Force found insufficient evidence that ABI screening reduced PAD or cardiovascular-related morbidity and mortality to support broad use, citing need for assessment in high-risk populations.[6] Targeted PRS testing based on age and clinical features could identify more high-risk individuals and facilitate earlier detection and initiation of preventative therapies, which are underused in PAD.[24] In our analysis of individuals at high genetic risk, nonsmoking was associated with a reduced risk of incident PAD compared to active smokers, which aligns with prior work that suggests genetic risk can be offset by modifiable lifestyle factors.[29,30] Conversely, statin and antithrombotic use were associated with increased incident PAD risk, which likely reflects the high risk of individuals that were prescribed preventive therapies and is confounded by their nonrandom allocation. In post hoc analyses of randomized trials, individuals at high genetic risk were found to derive greater relative and absolute benefit from statin therapy in primary prevention of CAD.[31] Future research should address the prospective effect of polygenic scores on hard PAD outcomes to examine if those at high genetic risk derive a similarly enhanced clinical benefit.

Our study demonstrates the potential of using genetic risk for major adverse limb event risk stratification. Secondary prevention efforts in PAD focus on limb salvage. Major adverse limb events represent index events for hospitalizations, reinterventions, major adverse cardiac events, and mortality[32]; however, there are no current vetted clinical tools for predicting major adverse limb events early in the disease course.[3] PRS-PAD consistently stratified future major adverse limb events risk in 3 distinct PAD cohorts. This highlights the promise for implementation of polygenic scores into secondary prevention measures, such as in guiding more aggressive or prolonged antithrombotic therapies that reduce the incidence of major adverse limb events.[32,33]

Limitations

Our study has several limitations. Although we incorporated GWAS results from multiple populations, our score is still limited by the constraints of existing data. Discovery GWAS data were largely Eurocentric, and PRS-PAD was fine-tuned in a European sample due to insufficient sample size of other ancestries, which together largely explains why PRS performance was reduced in non-European groups. This study was also restricted to single-ancestry individuals and had limited cases of East Asian and Middle Eastern and North African groups. Tailoring of polygenic scores to non-European target data, enhanced recruitment of underrepresented populations in biobanks, and development of methods to account for admixture should be priorities to improve PRS performance. PAD and major adverse limb events phenotyping was based on EHR diagnosis and procedures codes. There could have been variation in the quality of definitions between cohorts that influenced analyses toward null associations. However, we used noninvasive studies in the MGBB as another surrogate for PAD and observed similar associations of polygenic risk with binary classifications.

Conclusions

This cohort study showed that a new polygenic score estimated PAD and identified more cases of incident PAD when added to screening criteria. PRS-PAD also stratified risk for incident major adverse limb events in 3 cohorts with PAD. These results lay the groundwork for ongoing efforts to refine performance of polygenic scores for PAD.

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