Multi-ancestry polygenic risk scores for the prediction of type 2 diabetes and complications in diverse ancestries

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Summary

Background Polygenic risk scores (PRSs) improve prediction of the development of type 2 diabetes over the use of clinical risk factors alone; however, they perform poorly in populations of non-European ancestry, limiting their global clinical utility. We aimed to deliver comprehensive and rigorously tested multi-ancestry PRSs for prediction in type 2 diabetes.

Methods We conducted meta-analyses using data from type 2 diabetes genome-wide association studies (GWAS) across cohorts from five major global ancestries: European, African or African American, Admixed American, South Asian, and East Asian. We used summary statistics from the GWAS to construct single-ancestry PRSs (using the continuous-shrinkage PRS-CS method) and multi-ancestry PRSs (using the PRS-CSx method), and constructed ancestry-specific linkage disequilibrium panels to model pairwise correlations between single-nucleotide polymorphisms in GWAS during PRS construction. Models were validated for association with type 2 diabetes in at least four independent cohorts per ancestry. The effect sizes of PRSs were estimated as the odds ratio (OR) per SD of the PRS, and ORs for individuals at the 90th, 95th, and 97·5th PRS percentiles were compared with the IQR as a reference. We also tested our PRS models for prediction of diabetes incidence with or without additional clinical factors, as well as microvascular complications and comorbidities.

Findings Our analysis used data from 409 959 individuals with type 2 diabetes and 1 983 345 controls: respectively, 359 819 and 1 825 729 indivduals were included in the GWAS dataset, with 10 992 and 31 792 individuals in the training dataset and 39 148 and 125 824 individuals in the validation dataset. The best predictive performance for the single-ancestry PRSs was in European (incremental AUC 0·07–0·14) and East Asian (0·02–0·16) ancestries, whereas prediction was poorer for African or African American (0·02–0·03), Admixed American (0·02–0·04), and South Asian (0·02–0·04) ancestries, correlating with sample sizes in the GWAS. Compared with single-ancestry PRSs, our multi-ancestry PRSs showed higher effect sizes and smaller 95% CIs across all ancestries: OR per SD 1·73 (95% CI 1·67–1·80) in African or African American, 2·82 (2·67–2·97) in Admixed American, 2·45 (2·36–2·54) in East Asian, 2·36 (2·32–2·41) in European, and 2·23 (2·05–2·42) in South Asian ancestries. Individuals in the 97·5th PRS percentile had a 3–7 times increased risk of type 2 diabetes compared with those in the IQR (OR 3·43 [95% CI 2·80–4·21] in African or African American, 7·47 [5·64–9·89] in Admixed American, 6·62 [5·58–7·85] in East Asian, 6·25 [5·72–6·82] in European, and 4·50 [2·70–7·53] in South Asian ancestries). These PRSs were also associated with earlier onset of type 2 diabetes, higher risk of developing microvascular complications, and provide additional predictive value beyond clinical factors. In individuals with type 2 diabetes, the association between multi-ancestry PRSs and risk of microvascular complications and comorbidity was studied in populations of African, Admixed American, and European ancestries and was significant in all three ancestry groups for diabetic retinopathy (ORs per SD 1·28–1·57), diabetic nephropathy (1·25–1·58), proliferative diabetic retinopathy (1·39–2·08), and end-stage diabetic nephropathy (1·44–1·87); PRS was associated with coronary artery disease in the Admixed American ancestry group only (1·16 [95% CI 1·08–1·25]).

Interpretation These validated, publicly available PRSs can improve risk stratification for type 2 diabetes onset and complications across diverse ancestries, supporting their further evaluation in clinical settings.

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Research in context

Evidence before this study

Dozens of genome-wide association studies (GWAS) have been conducted for type 2 diabetes, generating vast amounts of genetic data used to construct polygenic risk scores (PRSs). These scores aggregate thousands of genetic variants to estimate an individual's genetic predisposition to type 2 diabetes. However, more than 70% of the data underpinning these risk scores originate from populations of primarily European ancestry. This ancestral bias fundamentally restricts the wide clinical applicability of PRSs, as their predictive performance decreases in non-European populations, including those of African or African American, South Asian, and Admixed American descent, in whom the burden of type 2 diabetes is often disproportionately high. Before this work, there was a deficit of robustly developed and extensively validated PRSs for type 2 diabetes that perform consistently across diverse ancestries. We searched the PGS Catalog for English-language publications, published between Oct 15, 2019, and Oct 7, 2024, reporting "type 2 diabetes" PRSs. Excluding process-specific PRSs or PRSs trained with data from the All of Us Research Program, we identified 25 papers detailing 55 PRSs published by our methodological cutoff to benchmark against our PRS models. Of these 25 studies, 12 relied entirely on GWAS from populations of European ancestry. Although 18 studies evaluated the PRSs across multiple ancestries, ten of these cross-ancestry studies still derived the PRSs from European GWAS. Overall, the sample sizes of the GWAS reached up to 1·1 million individuals, yet ancestry diversity was poor.

Added value of this study

This study leveraged the wealth of accumulated genetic data on individuals with type 2 diabetes to construct, train, and validate what are, to our knowledge, the most comprehensive PRSs applicable to five major global ancestry groups (African or African American, Admixed American, East Asian, European, and South Asian). Our multi-ancestry PRSs had better predictive ability for type 2 diabetes risk than our single-ancestry PRSs as well as other previously available PRSs, and could also predict an individual's risk of developing common microvascular complications and provide additional risk information beyond what traditional clinical factors alone can offer.

Implications of all the available evidence

PRSs are powerful tools that can significantly improve risk prediction when used alongside traditional clinical factors. However, to be clinically useful and equitable, they must work reliably for everyone. This study developed and rigorously tested PRSs to accurately identify individuals at high risk of type 2 diabetes and its complications from five major ancestry groups worldwide. By making these scores freely available, we provide researchers and clinicians with a resource that could help to advance genetic risk stratification and make type 2 diabetes prevention strategies more precise and globally fair.

Introduction

Type 2 diabetes is a major health problem. Approximately 589 million people are living with the condition globally, with numbers predicted to increase to 853 million by 2050.[1] Both genetic and environmental factors contribute to susceptibility to type 2 diabetes. Genome-wide association studies (GWAS) have identified 1289 genetic signals for the condition in individuals from diverse ancestries.[2,3] The aggregation of risk alleles in polygenic risk scores (PRSs) for type 2 diabetes[2,4] could provide insights into disease progression and prognosis, and identify people at risk of developing the condition for prioritisation of therapeutic or lifestyle interventions.[5] Several initiatives have tested the use of PRSs in clinical settings,[6,7] and have shown that PRSs for type 2 diabetes are particularly valuable for identifying individuals at risk among those perceived to be at low risk on the basis of standard clinical risk factors.[8]

Type 2 diabetes and related complications disproportionately affect populations of South Asian, African American, and Hispanic or Latin American ancestries compared with those of European ancestry.[9] However, most PRSs are based on GWAS comprising predominantly individuals of European ancestry and have poor performance in individuals of other ancestries, which could further exacerbate health disparities if PRSs were used for disease prediction in diverse populations.[2,10]

Research efforts over the past 7 years have aimed to improve the transferability of PRSs across diverse ancestries. First, the Polygenic Risk Methods Development (PRIMED) consortium and others have developed new methods, such as those incorporating GWAS and linkage disequilibrium data from multiple ancestries, showing improved prediction.[11,12] Second, data from large-scale GWAS of type 2 diabetes in non-European populations have become available, which could improve the power of PRSs in these populations. Third, the emergence of large-scale biobank data, such as from the All of Us Research Program, provides independent samples from diverse ancestries that could be used to develop, train, and validate novel PRSs.[13,14]

As part of the Type 2 Diabetes Global Genomics Initiative (T2DGGI), we published the largest meta-analysis of multi-ancestry GWAS of type 2 diabetes to date, including data from 2·5 million individuals.[3] Here we present results from Diabetes Polygenic Risk Scores in Multiple ancestries (D-PRISM),[2,12] an international consortium to develop PRSs for different types of diabetes and disease progression across the lifespan in diverse ancestries. We aimed to leverage the T2DGGI and the D-PRISM consortia to aggregate data from type 2 diabetes GWAS from five major ancestry groups, and to

train and validate PRS models in independent cohorts to evaluate the performance of these scores in predicting type 2 diabetes, its complications, and comorbidities using a unified pipeline. We tested the optimal PRS models for each ancestry and have made them available to the community for future testing of their clinical utility.

Methods

Study design and participants

The overall study design is detailed in appendix 1 (pp 1–6). We used type 2 diabetes GWAS data from selected cohorts participating in three large consortia: Diabetes Meta-analysis of Trans-ethnic Association Studies,[15] Million Veteran Program,[16] and FinnGen.[17] Cohorts were categorised by genetic similarity to the 1000 Genomes project[18] or to the predominant major global ancestry group according to the country of origin: African or African American, Admixed American, East Asian, European, and South Asian. We leveraged nearly all available genetic datasets with type 2 diabetes phenotype information for the following purposes: to maximise diversity in ancestries, harmonising 125 type 2 diabetes GWAS datasets including up to 2·2 million individuals (appendix 2 tabs 1, 2); to enhance the representation and tagging of the genetic variants contributing to the PRSs by generating new, ancestry-specific linkage disequilibrium reference panels (appendix 2 tab 7); to train PRS models across ancestries (appendix 2 tabs 3, 4); and to thoroughly validate the PRSs in multiple independent, harmonised cohorts (appendix 2 tabs 5, 6) and to assess the association of these PRSs with diabetes-related complications and comorbidities (appendix 2 tabs 13, 14). All studies were approved by local institutional review boards and/or ethics committees (appendix 1 pp 33–38).

Procedures

We used summary statistics from ancestry-specific type 2 diabetes GWAS to construct single-ancestry PRSs, using the continuous-shrinkage PRS-CS[19] method, and multi-ancestry PRSs, using the PRS-CSx[20] method. The PRS-CSx approach uses the increased statistical power from GWAS of five major ancestry groups, which are jointly modelled to maximise the power of variants present in all ancestries as well as incorporating ancestry-specific effects. Ancestry-specific linkage disequilibrium panels were used to model pairwise correlations between single-nucleotide polymorphisms (SNPs) in GWAS during PRS construction. The original linkage disequilibrium panels are based on SNPs derived from the International HapMap Project phase 3 data (HapMap3), which do not tag well in non-European populations. In addition, the original linkage disequilibrium panels used samples from the 1000 Genomes project, which has a limited number of samples, or the UK Biobank, which has only a small amount of data from individuals with non-European ancestry. To improve tagging, we developed new linkage disequilibrium panels with an expanded set of SNPs generated using the Tag(ging) It(erative) of SNPs in multiple populations (TagIt) program[21] for variants with ancestry-specific minor allele frequencies of at least 0·01 in the 1000 Genomes project. We also used more than 8000 in-house samples to compute ancestry-specific pairwise linkage disequilibrium, which enables more accurate linkage disequilibrium modelling (appendix 2 tab 7).

Statistical analysis

We compared the effect of ancestry in GWAS, SNP sets, and linkage disequilibrium sources on PRS performance in the training cohorts. We defined the best models as those that maximised the incremental area under the curve (iAUC) for predicting prevalent type 2 diabetes (appendix 2 tab 8). To calculate the iAUC, we subtracted the AUC of a model without the PRS from the AUC of a full model that included the PRS, sex, age, and genetic principal components. We validated the best-performing models in at least four independent cohorts per ancestry and fitted secondary models with BMI as an additional covariate (appendix 2 tabs 9, 10). We estimated the effect size of PRSs as the odds ratio (OR) per SD of the PRS, and calculated ORs for individuals at the 90th, 95th, and 97·5th PRS percentiles compared with the IQR reference. We used the DeLong test to compare the iAUCs of single-ancestry and multi-ancestry PRSs. We combined the PRS estimates across validation cohorts using fixed-effects meta-analyses by ancestry, weighting each cohort's β coefficient by its inverse variance via the metafor package in R.

In the All of Us version 7 cohort, we compared our best-performing type 2 diabetes PRSs with 55 scores from the Polygenic Score (PGS) Catalog. We defined statistical significance using a Bonferroni-corrected threshold of $p<0·0009$ (0·05 / 55) to account for multiple testing. We also compared different strategies for PRS construction. Although some studies leverage ancestry diversity using inverse-variance-weighted meta-analysis from multi-ancestry GWAS—typically using a single European linkage disequilibrium panel—this approach might not accurately model linkage disequilibrium patterns or tag ancestry-specific variants. To evaluate the PRS-CSx approach against standard meta-analysis, we conducted an inverse-variance-weighted meta-analysis of D-PRISM ancestry-specific GWAS summary statistics and applied PRS-CS using the European 1000 Genomes Project HapMap3 linkage disequilibrium reference panel. We also evaluated PRSs based on the largest meta-analysis of multi-ancestry GWAS of type 2 diabetes, conducted by Suzuki and colleagues,[3] which included a sample size 16% larger than our datasets, as we intentionally held out several cohorts for PRS training and validation. For these PRSs based on data from Suzuki and colleagues, we either applied PRS-CS or

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constructed a restricted-to-significance PRS using 1289 distinct type 2 diabetes variants (appendix 2 tab 11).

Type 2 diabetes adversely affects the functions of multiple organs, leading to long-term complications and comorbidities.[23] We used data from the All of Us version 8 cohort to assess the utility of the best-performing multi-ancestry PRSs in identifying individuals with type 2 diabetes who are at risk of developing microvascular complications (diabetic retinopathy, proliferative diabetic retinopathy, diabetic nephropathy, and end-stage diabetic nephropathy) and comorbidities (coronary artery disease and ischaemic stroke). We fitted logistic regression models adjusted for sex, age, and genetic principal components, focusing our subsequent analyses on African or African American, Admixed American, and European ancestries, for which sample sizes in the All of Us cohort were sufficient. To determine if the duration of type 2 diabetes mediated these effects, we conducted two sensitivity analyses: first, we restricted the sample to patients in whom the onset of type 2 diabetes preceded the first record of the complication; second, we adjusted for the estimated duration of type 2 diabetes (appendix 2 tabs 12, 13).

Finally, to better assess the clinical impact of the PRSs, we extracted electronic health record data to implement a comprehensive clinical risk score based on the type 2 diabetes Framingham Risk Score. This score comprised nine components: age, sex, parental history of type 2 diabetes, BMI, systolic blood pressure, and high-density lipoprotein, total cholesterol, triglycerides, and random glucose concentrations. We conducted Kaplan–Meier analysis to estimate diabetes-free survival across PRS tertiles and used Cox proportional hazards models to quantify the predictive value of the PRSs for incident type 2 diabetes, evaluating the score both as a stand-alone predictor and in combination with the nine-component clinical risk score. To evaluate if the PRSs provided predictive value independent of glucose concentration, we fitted Cox models using the lowest

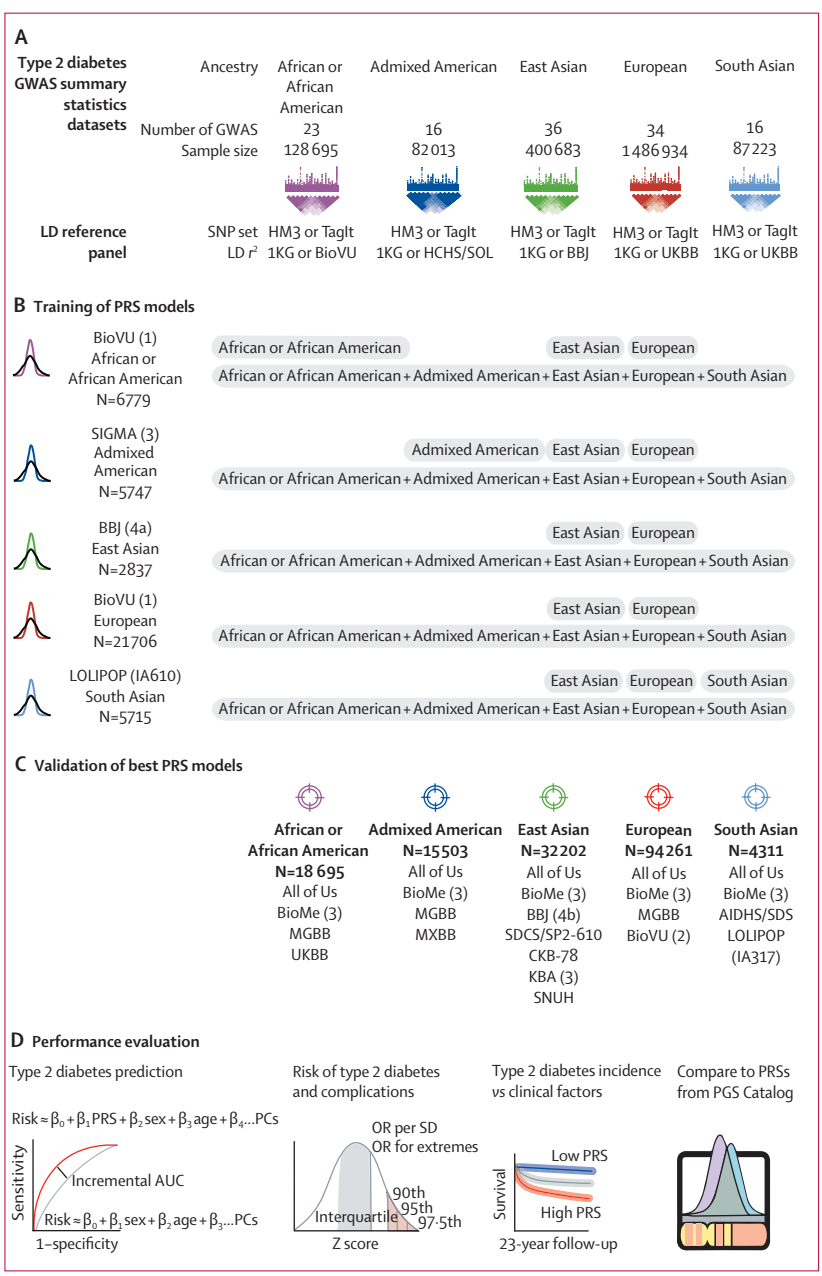
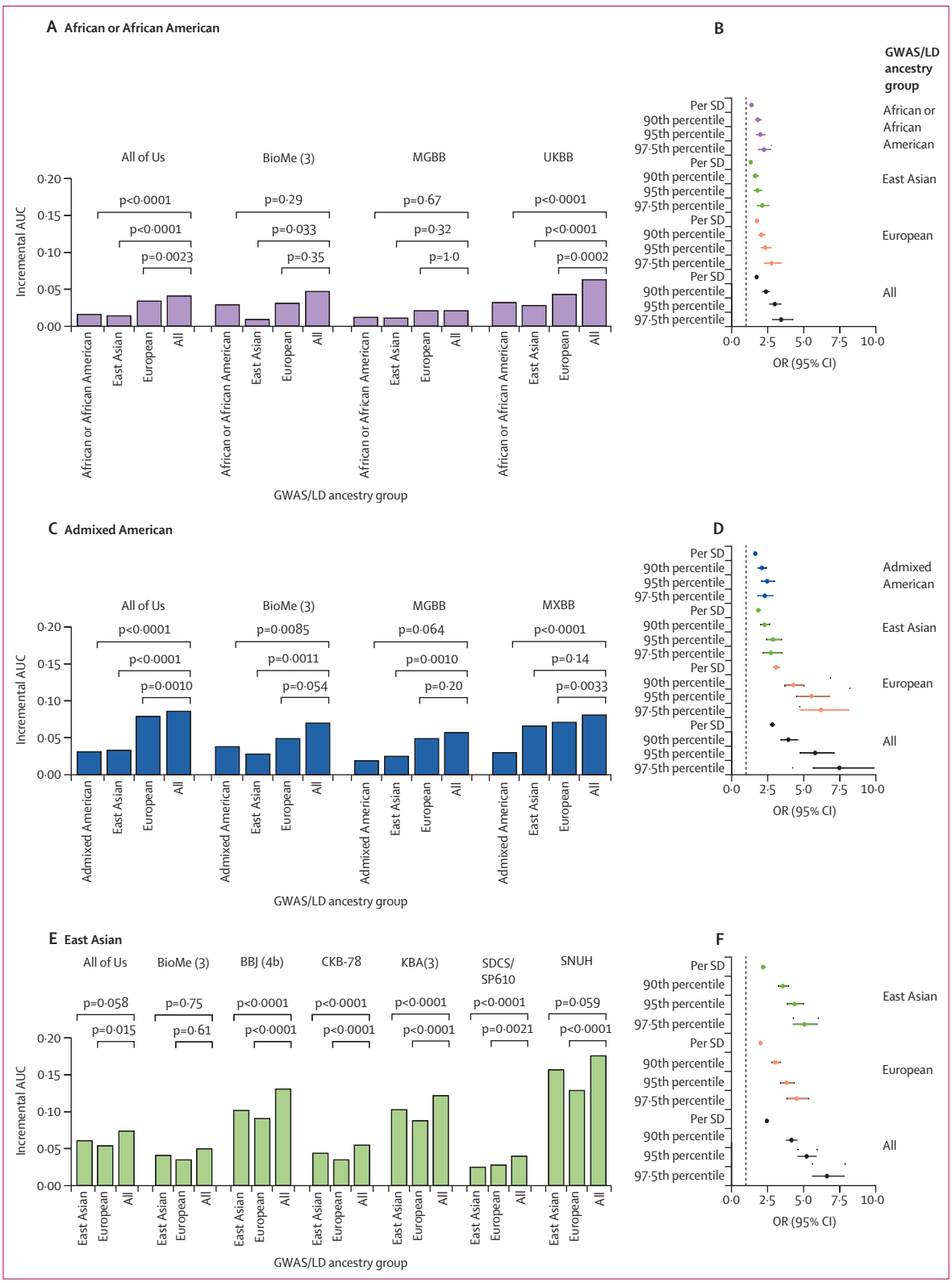


Figure 1: **Overall analysis approach**
(A) Overview of the 125 type 2 diabetes GWAS datasets, SNP sets, and pairwise LD information used to generate five ancestry-specific type 2 diabetes GWAS meta-analyses and 20 LD reference panels for PRSs training (appendix 1 p 1). (B) Independent, ancestry-specific cohorts used to train the PRS models and select the optimal continuous shrinkage prior from five ϕ values (0·01, 0·001, 1×10^{-4}, 1×10^{-5}, and 1×10^{-6}) based on predictive performance. Single-ancestry PRSs used GWAS summary statistics and LD panels matched to the validation ancestry or used data from East Asian or European ancestry datasets. Multi-ancestry PRSs jointly modelled GWAS summary statistics and LD panels from all five ancestry groups. (C) Set of 23 ancestry-specific and independent cohorts used to validate the 18 best-performing PRSs. (D) Evaluation of PRS predictive performance: incremental AUC, calculated as the difference between the AUC of the full model (risk ≈ β_0 + β_1 PRS + β_2 sex + β_3 age + β_4 ... PCs) and the model without the PRS (risk ≈ β_0 + β_1 sex + β_2 age + β_3 ... PCs), and the proportion of variation in type 2 diabetes status explained by the PRS, estimated using the difference between the Nagelkerke's r^2 of the full model (risk ≈ β_0 + β_1 PRS + β_2 sex + β_3 age + β_4 ... PCs) and the model without the PRS (risk ≈ β_0 + β_1 sex + β_2 age + β_3 ... PCs); the OR per SD of the PRS distribution or OR comparing PRS distribution extremes relative to the IQR; diabetes-free survival probabilities over 23 years of follow-up, estimated using Kaplan–Meier curves stratified by PRS tertile; and a comparative benchmarking of the best-performing multi-ancestry PRS against 55 existing type 2 diabetes PRSs from the PGS Catalog (appendix 1 pp 1–4). 1KG=1000 Genomes. AIDHS/SDS=Asian Indian Diabetic Heart Study/Sikh Diabetes Study. AUC=area under the curve. BBJ=BioBank Japan. BioMe=BioMe Biobank. BioVU=Vanderbilt University Medical Center. CKB-78=China Kadoorie Biobank. GWAS=genome-wide association studies. HCHS/SOL=Hispanic Community Health Study/Study of Latinos. HM3=HapMap3. KBA=Korea Biobank Array. LD=linkage disequilibrium. LOLIPOP=London Life Sciences Prospective Population. MGBB=Mass General Brigham Biobank. MXBB=Mexican Biobank. OR=odds ratio. PCs=principal components. PGS=polygenic score. PRS=polygenic risk score. SDCS/SP2-610=Singapore Diabetic Cohort Study and Singapore Prospective Study Program. SIGMA=Slim Initiative for Genomic Medicine in the Americas. SNP=single-nucleotide polymorphism. SNUH=Seoul National University Hospital. TagIt=Tag(ging) It(erative) of SNPs in multiple populations. UKBB=UK Biobank. Numbers in parentheses represent different subset of data used in a cohort.



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See Online for appendices 1 and 2

(Figure 2 continues on next page)

PRS tertile and random glucose concentration of less than 140 mg/dL as the reference group (appendix 2 tabs 14, 15). We conducted all statistical analyses using R version 4.3.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Compared with those based on HapMap3, the new linkage disequilibrium panels generated using TagIt improved the overall SNP coverage of variants from the 1000 Genomes Project by up to two times. Coverage increased by seven times for SNPs with minor allele frequencies of 0·01–0·05 in individuals with African or African American ancestry (appendix 1 pp 6, 7, appendix 2 tab 7). In all ancestry groups, the best-performing PRSs were those constructed using the expanded TagIt set of variants and/or the recomputed in-house pairwise linkage disequilibrium with large sample sizes (appendix 1 p 7, appendix 2 tab 8), suggesting that higher SNP coverage and better linkage disequilibrium modelling improve prediction.

In the ancestry-specific meta-analyses, we included 2 185 548 individuals (359 819 with type 2 diabetes and 1 825 729 controls) from 125 type 2 diabetes GWAS datasets (34 European, 36 East Asian, 23 African or African American, 16 Admixed American, and 16 South Asian; figure 1A, appendix 2 tabs 1, 2). To train PRSs (ie, tuning PRS construction parameters) we used

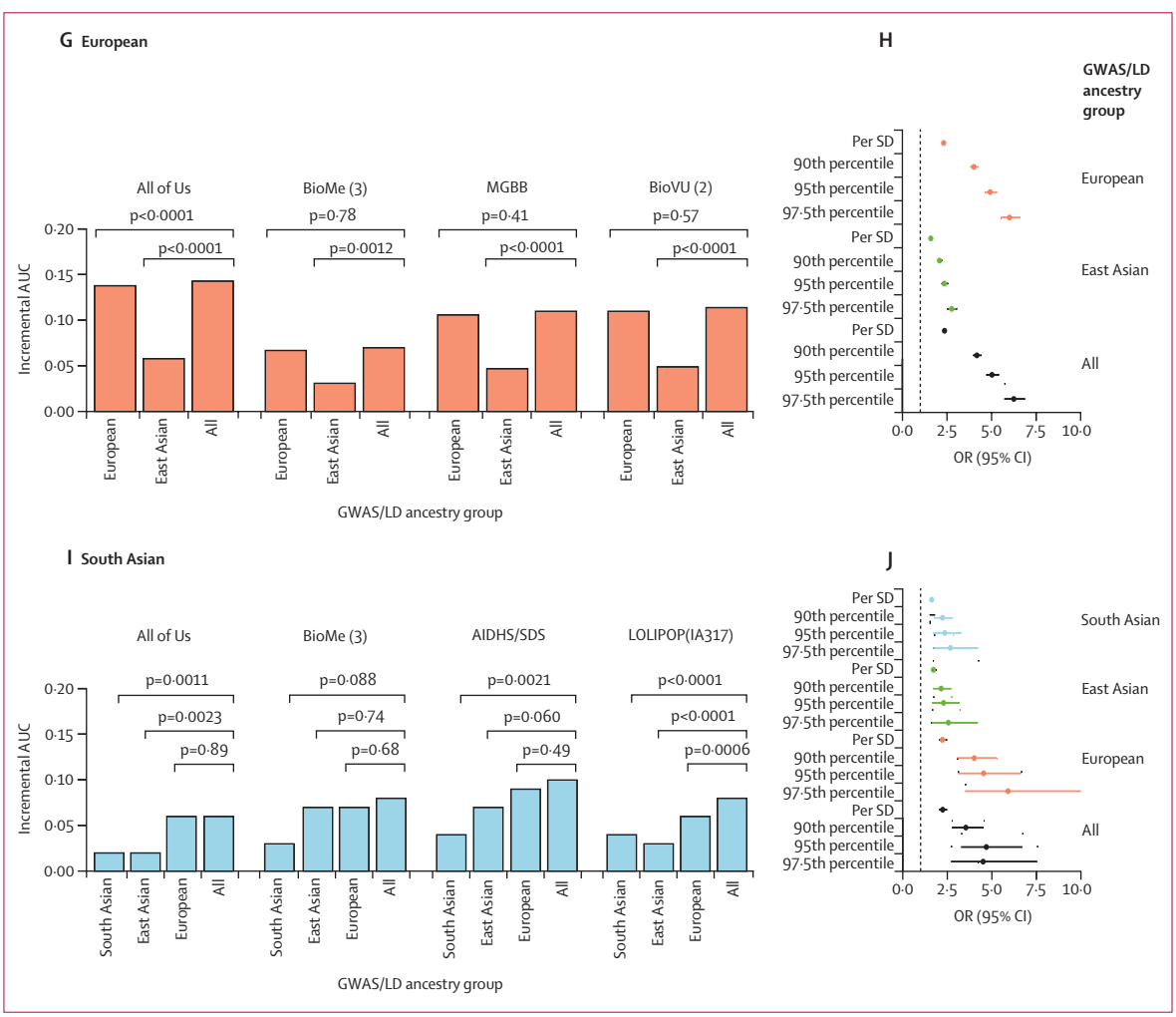

Figure 2: **Performance of the type 2 diabetes PRSs in the validation cohorts across ancestry groups**

Incremental AUC of the type 2 diabetes PRSs in the validation cohorts across ancestry groups: African or African American (A), Admixed American (C), East Asian (E), European (G), and South Asian (I). For each ancestry, the best-performing single-ancestry and multi-ancestry PRSs were evaluated. Each bar represents a single cohort. Odds ratio from the meta-analysis of validation cohorts across ancestry groups: African or African American (B), Admixed American (D), East Asian (F), European (H), and South Asian (J). Points represent the OR per SD of the PRS distribution or the OR comparing different PRS distribution extremes (90th, 95th, and 97·5th percentiles) relative to the IQR. Error bars show the 95% CIs. The dashed lines indicate an OR of 1. All models were adjusted for sex, age, and genetic principal components. AUC=area under the curve. GWAS=genome-wide association studies. LD=linkage disequilibrium. OR=odds ratio. PRS=polygenic risk score.

one independent cohort per ancestry, aggregating data from 42 784 individuals (10 992 with type 2 diabetes and 31 792 controls; figure 1B, appendix 2 tabs 3, 4), and for validation (ie, testing PRS performance) we used at least four cohorts per ancestry, including data from 164 972 individuals (39 148 with type 2 diabetes and 125 824 controls; figure 1C, appendix 2 tabs 5, 6).

We first trained PRSs (appendix 2 tabs 3, 4) using GWAS summary statistics and four linkage disequilibrium panels, each matched to the ancestry of validation cohorts (appendix 2 tabs 5, 6). The performance of the matched single-ancestry PRS was positively correlated with the sample sizes of the GWAS. The best predictive performance was observed in European (incremental AUC 0·07–0·14) and East Asian (0·02–0·16) ancestries, whereas prediction was poorer for African or African American (0·02–0·03), Admixed American (0·02–0·04), and South Asian (0·02–0·04; figure 2, appendix 2 tab 9) ancestries.

We also observed larger effect sizes in European (OR per SD 2·31 [95% CI 2·26–2·35]) and East Asian (2·19 [2·12–2·27]) validation cohorts than in African or African American (1·38 [1·34–1·43]), Admixed American (1·64 [1·57–1·71]), and South Asian (1·61 [1·50–1·74]) cohorts. The PRSs for European and East Asian ancestries also had better power for the identification of individuals at very high risk of developing type 2 diabetes. Individuals at the 90th percentile of the PRS distribution had an approximately 3·5–4 times increased risk of type 2 diabetes compared with those in the IQR in European (OR 4·01 [95% CI 3·82–4·21]) and East Asian (3·58 [3·24–3·94]) ancestries, compared with an approximately two times increased risk in African or African American (1·82 [1·64–2·01]), Admixed American (2·10 [1·84–2·39]), and South Asian (2·22 [1·75–2·81]) ancestries (figure 2, appendix 2 tab 9). We observed similar results regardless of adjustment for BMI (appendix 1 p 8, appendix 2 tab 10).

We tested whether constructing PRSs using GWAS summary statistics from ancestries with larger sample sizes, such as European and East Asian, could improve the prediction of type 2 diabetes risk in ancestries with smaller GWAS sample sizes, despite ancestral differences between the discovery and validation cohorts. Compared with the matched single-ancestry PRSs, the use of European GWAS improved type 2 diabetes risk prediction in African or African American, Admixed American, and South Asian validation cohorts, but gave poorer predictions in East Asian validation cohorts. The PRS based on East Asian GWAS showed a small improvement in prediction of type 2 diabetes risk in Admixed American and South Asian validation cohorts, but poorer performance in African or African American and European validation cohorts (figure 2, appendix 2 tab 9). The effect sizes of the PRSs were consistent with their prediction performance. The PRS using European GWAS was the best-performing single-ancestry PRS for African or African American (OR per SD 1·75 [95% CI 1·67–1·82]), Admixed American (3·07 [2·89–3·27]), South Asian (2·21 [2·03–2·42]), and European (2·31 [2·26–2·35]) cohorts, whereas the PRS using East Asian GWAS had the best performance in East Asian cohorts (2·19 [2·12–2·27]; figure 2, appendix 2 tab 9).

We further applied PRS-CSx[20] to develop multi-ancestry PRSs. Compared with the best single-ancestry PRSs, multi-ancestry PRSs showed higher prediction performance across validation cohorts from all ancestries (AUC 0·63–0·75 and incremental AUC 0·02–0·06 in African or African American, 0·71–0·77 and 0·06–0·09 in Admixed American, 0·72–0·86 and 0·04–0·17 in East Asian, 0·69–0·76 and 0·07–0·14 in European, and 0·67–0·80 and 0·06–0·10 in South Asian cohorts; figure 2, appendix 2 tab 9).

The multi-ancestry PRSs also had higher effect sizes and smaller CIs than the single-ancestry PRSs across all ancestries (OR per SD 1·73 [95% CI 1·67–1·80] in African or African American, 2·82 [2·67–2·97] in Admixed American, 2·45 [2·36–2·54] in East Asian, 2·36 [2·32–2·41] in European, and 2·23 [2·05–2·42] in South Asian ancestries). The improvement was particularly notable for individuals at the extremes of PRS distributions. Individuals in the 97·5th percentile of the multi-ancestry PRSs had a 3–7 times increased risk of type 2 diabetes than those in the IQR (OR 3·43 [95% CI 2·8–4·21] in African or African American, 7·47 [5·64–9·89] in Admixed American, 6·62 [5·58–7·85] in East Asian, 6·25 [5·72–6·82] in European, and 4·50 [2·70–7·53] in South Asian ancestry groups; figure 2, appendix 2 tab 9).

We leveraged data from the All of Us Research Program to compare our best-performing multi-ancestry PRSs against the published type 2 diabetes PRSs from the PGS Catalog.[22] We tested 55 of 147 available PRSs for type 2 diabetes (accessed Oct 7, 2024), after excluding pathway-specific PRSs or those including data from the All of Us cohort in PRS development. The multi-ancestry PRSs showed significantly better predictive performance than those reported previously for the African or African American, Admixed American, and European ancestry groups (incremental AUC for our multi-ancestry PRSs *vs* best incremental AUC from the PGS Catalog: 0·041 *vs* 0·029 in African or African American, 0·086 *vs* 0·073 in Admixed American, and 0·143 *vs* 0·123 in European ancestries; DeLong p<0·0009, Bonferroni correction for 55 tests) but not for the East Asian (0·074 *vs* 0·062) and South Asian (0·061 *vs* 0·068) ancestry groups (DeLong p>0·0009; appendix 1 pp 9–14, appendix 2 tab 11).

To assess the utility of the PRS-CSx method, we constructed a PRS-CS model using summary statistics from the inverse variance-weighted GWAS meta-analysis of our ancestry-specific GWAS summary statistics and tested its performance in the All of Us cohort. The performance of the multi-ancestry PRS-CSx

models was significantly higher than that of the PRS-CS models in the prediction of type 2 diabetes risk for Admixed American, East Asian, and European ancestry groups (incremental AUC for multi-ancestry PRS-CSx *vs* multi-ancestry PRS-CS: 0·086 *vs* 0·077 in Admixed American, 0·074 *vs* 0·061 in East Asian, and 0·143 *vs* 0·126 in European ancestries; DeLong p<0·05) but not for African or African American (0·041 *vs* 0·038) and South Asian (0·061 *vs* 0·060) ancestry groups (DeLong p>0·05) (appendix 1 pp 9–14, appendix 2 tab 11).

We also showed that, despite being based on a smaller sample of GWAS, our multi-ancestry PRS-CSx model showed higher predictive performance than the PRS-CS model for the dataset from Suzuki and colleagues in the Admixed American, European, and East Asian ancestry groups (incremental AUC for our multi-ancestry PRS-CSx *vs* Suzuki and colleagues PRS-CS: 0·086 *vs* 0·077 in Admixed American, 0·074 *vs* 0·059 in East Asian, and 0·143 *vs* 0·128 in European, DeLong p<0·05) and similar predictive performance in the African or African American (0·041 *vs* 0·041) and South Asian (0·061 *vs* 0·068) ancestry groups (DeLong p>0·05; appendix 1 pp 9–14).

Additionally, our multi-ancestry PRS-CSx models showed consistently improved prediction performance in Admixed American (0·086 *vs* 0·054), East Asian (0·074 *vs* 0·042), European (0·143 *vs* 0·090), and South Asian (0·068 *vs* 0·034) ancestry groups (DeLong p<0·05), and similar performance in the African or African American ancestry group (0·041 *vs* 0·038; DeLong p>0·05), when compared with a multi-ancestry PRS that was restricted to the 1289 genome-wide significant variants identified by Suzuki and colleagues (appendix 1 pp 9–14, appendix 2 tab 11).[3]

In individuals with type 2 diabetes, our multi-ancestry PRS-CSx were significantly associated with increased risk of microvascular complications across the three ancestries studied (African or African American, Admixed American, and European). Effect sizes (OR per SD) ranged from 1·28 (95% CI 1·18–1·39; African or African American) to 1·57 (1·43–1·73; Admixed American) for diabetic retinopathy and from 1·25 (1·18–1·32; European) to 1·58 (1·41–1·78; Admixed American) for diabetic nephropathy, and were higher for the more severe forms, proliferative diabetic retinopathy (1·39 [1·17–1·65; African or African American] to 2·08 [1·73–2·51; Admixed American]) and end-stage diabetic nephropathy (1·44 [1·20–1·74; African or African American] to 1·87 [1·56–2·22; Admixed American]; p<0·008, Bonferroni correction for six outcomes). Conversely, the PRS was associated with coronary artery disease in the Admixed American ancestry group only (OR 1·16 [95% CI 1·08–1·25]; figure 3, appendix 2 tabs 12, 13). Additional sensitivity analyses revealed an association between PRS and earlier age of onset of type 2 diabetes: a 1 SD increase in the PRS was associated with an earlier onset of type 2 diabetes of up to 2·3 years across the three genetic ancestries (appendix 1 p 16). Adjusting for the duration of type 2 diabetes, or restricting to individuals in which the onset of diabetes preceded the onset of complications on the basis of electronic health record data, yielded consistent results (appendix 1 pp 3–4, 15–16, appendix 2 tab 13).

Over a median follow-up of 7·4 years (IQR 3·91–9·31; range 0·05–21·96), 2074 of 17 920 individuals developed incident type 2 diabetes and 15 846 remained disease-free (appendix 1 p 4, appendix 2 tabs 14–15). Kaplan–Meier analysis by PRS tertile showed significant, stepwise associations with disease-free survival across ancestries (figure 4; log-rank p<0·0001 for all). Compared with the lowest tertile (T1), the highest tertile (T3) had higher hazard ratios (HR 1·76 [95% CI 1·39–2·23] in African or African American, 3·87 [2·63–5·68] in Admixed American, and 5·26 [4·39–6·29] in European ancestries; appendix 2 tab 14). The PRSs provided predictive value independent of random glucose concentration, especially for individuals with high concentrations (≥140 mg/dL;

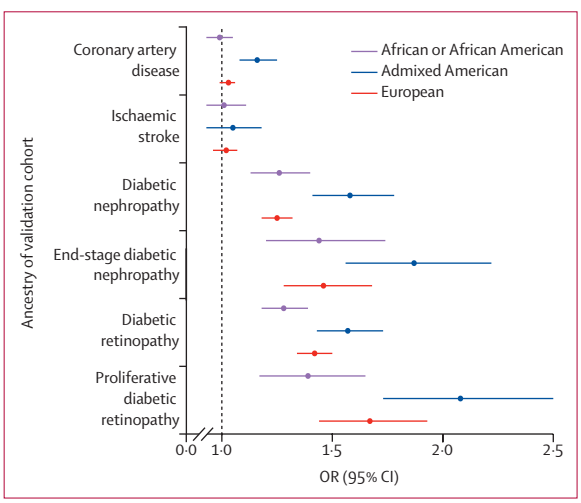

Figure 3: **Association of our multi-ancestry PRS with common complications and comorbidities of diabetes in the All of Us cohort**
ORs per SD increase for six outcomes in African or African American, Admixed American, and European cohorts: coronary artery disease, ischaemic stroke, diabetic nephropathy, end-stage diabetic nephropathy, diabetic retinopathy, and proliferative diabetic retinopathy. All analyses were restricted to individuals with type 2 diabetes. Error bars indicate 95% CIs. All models were adjusted for sex, age, and genetic principal components. OR=odds ratio. PRS=polygenic risk score.

Figure 4: **Kaplan–Meier curves by PRS tertile, stratified by ancestry and prediabetes status**
Diabetes-free survival analyses, without (left) and with (middle and right) stratification by prediabetes (random glucose concentration ≥140 mg/dL) status, by genetic ancestry group: African or African American (A), Admixed American (B), and European (C). Diabetes-free survival is stratified by PRS tertile (coloured lines), whereby increased colour intensity corresponds to higher genetic risk; 95% CIs are shaded. p values were derived from the log-rank test to assess differences in survival distributions across PRS tertiles. PRS=polygenic risk score. T1=tertile 1 (lowest tertile). T2=tertile 2 (middle tertile). T3=tertile 3 (highest tertile).

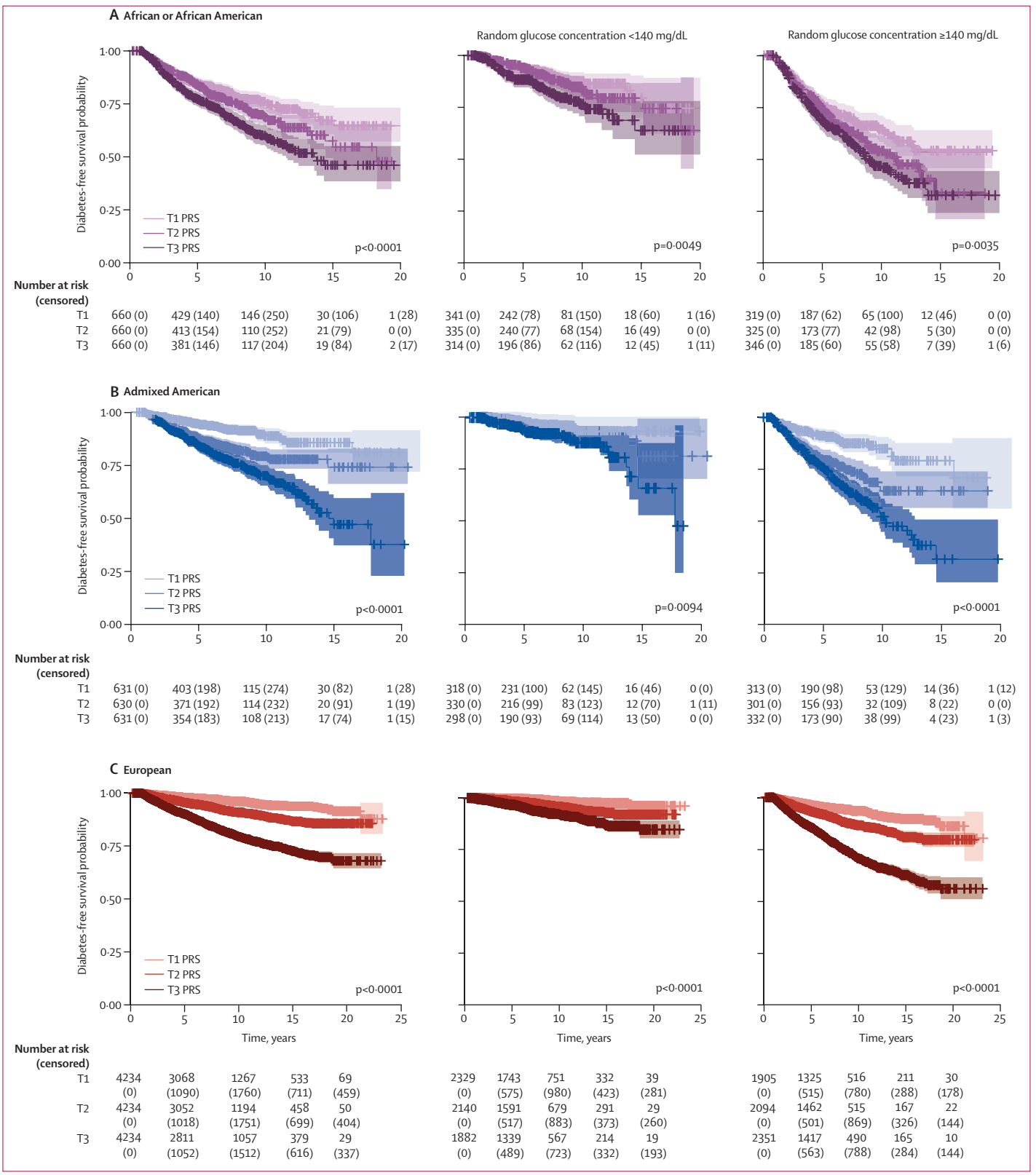
A African or African American
Random glucose concentration <140 mg/dL
Random glucose concentration ≥140 mg/dL
Diabetes-free survival probability
1·00
0·75
0·50
0·25
0·00
T1 PRS
T2 PRS
T3 PRS
p<0·0001
p=0·0049
p=0·0035
0
5
10
15
20
Number at risk (censored)
T1 660 (0) 429 (140) 146 (250) 30 (106) 1 (28) 341 (0) 242 (78) 81 (150) 18 (60) 1 (16) 319 (0) 187 (62) 65 (100) 12 (46) 0 (0)
T2 660 (0) 413 (154) 110 (252) 21 (79) 0 (0) 335 (0) 240 (77) 68 (154) 16 (49) 0 (0) 325 (0) 173 (77) 42 (98) 5 (30) 0 (0)
T3 660 (0) 381 (146) 117 (204) 19 (84) 2 (17) 314 (0) 196 (86) 62 (116) 12 (45) 1 (11) 346 (0) 185 (60) 55 (58) 7 (39) 1 (6)
B Admixed American
Diabetes-free survival probability
1·00
0·75
0·50
0·25
0·00
T1 PRS
T2 PRS
T3 PRS
p<0·0001
p=0·0094
p<0·0001
0
5
10
15
20
Number at risk (censored)
T1 631 (0) 403 (198) 115 (274) 30 (82) 1 (28) 318 (0) 231 (100) 62 (145) 16 (46) 0 (0) 313 (0) 190 (98) 53 (129) 14 (36) 1 (12)
T2 630 (0) 371 (192) 114 (232) 20 (91) 1 (19) 330 (0) 216 (99) 83 (123) 12 (70) 1 (11) 301 (0) 156 (93) 32 (109) 8 (22) 0 (0)
T3 631 (0) 354 (183) 108 (213) 17 (74) 1 (15) 298 (0) 190 (93) 69 (114) 13 (50) 0 (0) 332 (0) 173 (90) 38 (99) 4 (23) 1 (3)
C European
Diabetes-free survival probability
1·00
0·75
0·50
0·25
0·00
T1 PRS
T2 PRS
T3 PRS
p<0·0001
p<0·0001
p<0·0001
0
5
10
15
20
25
Time, years
Number at risk (censored)
T1 4234 (0) 3068 (1090) 1267 (1760) 533 (711) 69 (459) 2329 (0) 1743 (575) 751 (980) 332 (423) 39 (281) 1905 (0) 1325 (515) 516 (780) 211 (288) 30 (178)
T2 4234 (0) 3052 (1018) 1194 (1751) 458 (699) 50 (404) 2140 (0) 1591 (517) 679 (883) 291 (373) 29 (260) 2094 (0) 1462 (501) 515 (869) 167 (326) 22 (144)
T3 4234 (0) 2811 (1052) 1057 (1512) 379 (616) 29 (337) 1882 (0) 1339 (489) 567 (723) 214 (332) 19 (193) 2351 (0) 1417 (563) 490 (788) 165 (284) 10 (144)

figure 4; log-rank p<0·01). The risk of developing type 2 diabetes for individuals with both risk factors (ie, PRS T3 and high random glucose concentrations) was substantially higher than the risk for individuals with either factor alone, with HR 5·35 [95% CI 3·67–7·79) in African or African American, 13·82 [7·24–26·39] in Admixed American, and 22·43 [15·61–32·21] in European ancestry groups (appendix 2 tab 14). Similarly, in all ancestry groups, we observed that individuals who had normoglycaemia but were in the highest PRS tertile had a similar risk to individuals who were in the lowest PRS tertile but had random glucose concentrations of at least 140 mg/dL, a criterion in the definition of prediabetes.

The clinical risk score—including age, sex, parental history of type 2 diabetes, BMI, systolic blood pressure, and high-density lipoprotein, total cholesterol, triglyceride, and random glucose concentrations—had concordance indices of 0·73 for African or African American, 0·77 for Admixed American, and 0·83 for European ancestries (appendix 2 tab 15). After adjusting for clinical risk score, the PRS remained significantly associated with incident risk (HR 1·28 [95% CI 1·14–1·44] in African or African American, 1·71 [1·44–2·03] in Admixed American, and 1·81 [1·70–1·94] in European ancestries). This model, combining the PRS and clinical risk score in a multivariable hazards model, further improved the concordance indices in Admixed American (0·77 *vs* 0·78, DeLong p=0·038) and European (0·83 *vs* 0·85; DeLong p<0·0001) ancestries (appendix 2 tab 15).

Discussion

More than 100 PRSs for type 2 diabetes have been published,[22] yet most have low predictive performance in under-represented populations—partly due to the over-representation of European populations in type 2 diabetes GWAS and differential linkage disequilibrium patterns across ancestries. Populations in which PRSs are less predictive—including African or African American, Admixed American, and South Asian ancestry groups—are disproportionately affected by diabetes and its complications, highlighting the risk of exacerbating health disparities through the use of PRSs derived only from European GWAS.[12] To improve the transferability and predictive accuracy of PRSs across diverse populations, including those under-represented in GWAS, various multi-ancestry PRS methods have been developed, while more GWAS from populations with diverse ancestries are also becoming available.[3,15,16,24,25] Beyond large GWAS sample sizes, multiple large datasets are also essential for training and validating PRSs, and rigorous data aggregation and harmonisation following best practices are crucial to assess the accuracy of PRSs. In this study, we developed what are, to our knowledge, the most comprehensive PRSs for type 2 diabetes across five major global ancestries and conducted extensive evaluations.

As previously described,[11,26] we observed that PRSs have lower predictive accuracy when the validation samples are genetically distant from the discovery GWAS samples. However, because GWAS in under-represented populations have limited power and imprecise variant effect-size estimates, PRSs derived from European GWAS—for which the sample size was at least 12 times larger than GWAS in populations with African or African American, Admixed American, and South Asian ancestries—continue to outperform those derived from ancestry-matched GWAS in the respective populations. By contrast, European PRSs had poorer performance in populations of East Asian ancestry than matched-ancestry PRS, even though the East Asian GWAS dataset was four times smaller than the European GWAS dataset. This finding suggests that non-matched-ancestry PRSs (ie, those based on GWAS from an ancestry different from that of the validation cohort) improve performance only when the GWAS sample size in the non-matched ancestry is orders of magnitude larger than that of the matched-ancestry GWAS, despite the lack of power to capture ancestry-specific genetic effects. However, ancestry-matched GWAS have high accuracy when power is sufficient. The minimum ancestry-specific GWAS sample size for robust PRS prediction remains trait-dependent and ancestry-dependent and warrants further investigation. Regardless, we observe that for all ancestry groups—even European, which has the largest GWAS sample size[15]—the optimal strategy for PRS development is to combine PRSs from multiple ancestries, here using the PRS-CSx method. This approach leverages estimates from variants present in all ancestries while accounting for population-specific or enriched variants, therefore improving the overall accuracy of prediction.

Across all ancestries, multi-ancestry PRSs showed the strongest associations with type 2 diabetes risk at the distribution extremes. In European, East Asian, and Admixed American ancestries, individuals in the top 97·5th percentile had a seven-times higher risk of developing type 2 diabetes than individuals in the IQR. Despite lower representation in terms of GWAS, the multi-ancestry PRS still outperformed matched-ancestry PRSs for African or African American and South Asian ancestries. However, the overall performance was lower for these populations than for those of other ancestry groups, with individuals in the top 97·5th percentile having a 3–4-times higher risk of developing type 2 diabetes than those in the IQR. These results underscore that, despite improvements, a substantial performance gap remains for under-represented populations.

In the All of Us cohort, our multi-ancestry PRSs outperformed previously available type 2 diabetes PRSs, probably because we used, to our knowledge, the largest and most diverse GWAS dataset to date and multi-ancestry-based methods for PRS development. Additionally, we constructed these multi-ancestry PRSs

using a standardised and rigorous approach and tested them extensively across diverse ancestry groups, supporting their broader applicability. For example, the multi-ancestry PRSs outperformed PRSs derived from the largest trans-ancestry meta-analysis.[3] These findings underscore that, in addition to increasing representation in GWAS, jointly modelling GWAS and linkage disequilibrium panels across ancestries can enhance causal variant tagging, thereby improving predictive performance. By contrast, standard methods using multi-ancestry inverse variance-weighted GWAS meta-analysis results rely on a single linkage disequilibrium reference panel, and could fail to capture ancestry-specific linkage disequilibrium patterns, limiting prediction accuracy.

Previous studies have reported significant associations between type 2 diabetes PRSs, proliferative diabetic retinopathy, and end-stage diabetic nephropathy in diverse ancestries.[15,16] We extend these findings, showing that our multi-ancestry PRSs can predict microvascular complications (diabetic retinopathy, diabetic neuropathy, proliferative diabetic retinopathy, and end-stage diabetic nephropathy) in individuals with type 2 diabetes of African or African American, Admixed American, and European ancestries. Notably, these associations are independent of the duration of type 2 diabetes. Future work is needed to assess whether these associations are driven by specific type 2 diabetes subtypes and, if so, whether the associations vary by ancestry.[3,27]

Our work has limitations. First, although constructing multi-ancestry PRSs that include GWAS from diverse ancestries enables the capture of ancestry-specific effects, the SNP effect sizes are still strongly influenced by the largest European cohorts. Second, we acknowledge that using discrete population categories is suboptimal, as this does not fully capture heterogeneous ancestry, particularly in admixed populations. Newer methods that model both local and global ancestry continuously could be powerful,[11,26] but often require individual-level data, limiting their scalability. Our approach, although limited to discrete ancestral groups, enables us to leverage the wealth of data from large-scale GWAS summary statistics across multiple ancestries. As larger biobanks emerge and methodological challenges (eg, the accurate modelling of local ancestry in admixed populations) are solved, adopting continuous genetic ancestry methods or hybrid models will become the optimal choice.

Despite some concerns that PRSs add little value over the use of clinical risk factors, previous work shows that PRSs can help to identify individuals at high risk of developing type 2 diabetes among those who are clinically perceived as being at low risk, (eg, those who are young, lean, or who have sparse clinical data[8]), and can improve prediction compared with family history alone.[28] We found that higher multi-ancestry PRSs were associated with an earlier onset of type 2 diabetes of up to 2·3 years across the three studied ancestries, supporting their utility in identifying individuals at high risk before they accumulate clinical risk factors. Furthermore, our PRSs predicted the development of type 2 diabetes independently of a nine-component clinical risk score, and showed that individuals with the highest PRSs and high random glucose concentrations (≥140 mg/dL) were at higher risk of developing type 2 diabetes (eg, HR 13·82 [95% CI 7·24–26·39] in Admixed American populations) than individuals with normoglycaemia and low PRSs.

Ongoing randomised controlled trials are starting to evaluate PRS implementation in primary care.[7,29] Viable interventions require state-of-the-art type 2 diabetes PRSs, prioritising generalisability, portability across ancestries, and the feasibility of implementation. For example, Lennon and colleagues[6] prioritised a multi-ancestry type 2 diabetes PRS[30] trained using GWAS data from populations of European, East Asian, and African ancestries to propose a high-risk threshold at the 98th percentile. Compared with the remaining individuals not at high risk, this PRS threshold was associated with a 4·44-times increased risk of developing type 2 diabetes in populations of European ancestry and a 2·35-times increased risk in populations of African ancestry. Notably, our multi-ancestry PRSs showed consistently improved predictive performance in all studied ancestries over previously reported PRS. Compared with individuals with average genetic risk, those at the highest genetic risk cutoff (97·5th percentile) have ORs ranging from 3·43 to 7·47 across ancestries. In summary, we deliver a comprehensive and rigorously tested set of multi-ancestry PRSs for type 2 diabetes.

Contributors

JMM and MCYN conceptualised the study. JMM, MCYN, and AH-C supervised the implementation of research plans across teams. AH-C and JK led the data curation. RM, YL, KS, LEP, HKN, JC, SL, MR, KL, and KT curated data and conducted statistical analyses to validate the PRSs in independent cohorts. AKM supervised the analyses. CAA-S, LG-G, CG-V, CAH, YJK, SHK, AL, RJFL, AM-E, APM, LO, JIR, DS, TT-L, BFV, MV, RGW, ML, JEB, and XS provided necessary data and supervised different stages of the analyses. JK and AH-C conducted the initial statistical analyses, with JK conducting additional analyses during revisions. JMM, MCYN, AH-C, JK, and TG guided the interpretation of the results. TG contributed to the design of the methodology and developed PRS-CSx. JMM, MCYN, and AKM contributed to funding acquisition and project administration. JMM, MCYN, AH-C, JK, and TG wrote the initial draft of the manuscript, which was reviewed by JMM and MCYN; AH-C prepared the figures and tables and prepared the final version of the manuscript. JMM and MCYN had full access to all data in the study. JMM and MCYN accessed and verified the data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data are not available because they are subject to data protection laws and restrictions imposed by the relevant ethics committees to ensure the privacy of the study participants. The developed PRS weights are available without restrictions through the Polygenic Score Catalog (https://www.pgscatalog.org; publication ID PGP000773, score IDs PGS005353–5377). The linkage disequilibrium panels are available upon request. The analysis code is reported at https://github.com/ahuertach/D-PRISM-T2D-PRS.

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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Huerta-Chagoya A, Kim J, Mandla R, et al. Multi-ancestry polygenic risk scores for the prediction of type 2 diabetes and complications in diverse ancestries. *Lancet Diabetes Endocrinol* 2026; published online April 27. https://doi.org/10.1016/S2213-8587(25)00405-X.

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Supplementary methods

Type 2 diabetes GWAS meta-analyses used for the construction of the PRSs

We leveraged the T2D GWAS summary statistics from a subset of cohorts participating in three large Consortia: Diabetes Meta-analysis of Trans-ethnic Association Studies (DIAMANTE)[1], the Million Veteran Program (MVP)[2], and the FinnGen Study.[3] An independent subset of cohorts was selected for the development and validation of the PRSs. If a cohort was multi-ancestry, each individual was categorized by genetic similarity to one or more of the five ancestries available in the 1000 Genomes (1KG) Project[4] and/or the Human Genome Diversity Project[5] as reference panels: African/African American (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS). For single-ancestry cohorts, the grouping was based on the country of recruitment. We included 2,185,548 individuals (359,819 T2D cases and 1,825,729 controls) across 125 T2D GWAS to conduct ancestry-specific meta-analyses (figure 1A, appendix 2 tabs 1,2).

Each GWAS tested the association of the genetic variants with T2D adjusted for age, sex, the top genetic principal components (PCs), and cohort-specific covariates. We performed an inverse variance weighted (IVW) fixed-effect meta-analysis for each ancestry group with the METAL software.[6] We then applied quality control to keep biallelic, nonpalindromic SNPs in at least half of the effective sample size with a minor allele frequency (MAF) ≥0·01. For each ancestry-specific T2D GWAS meta-analysis, we intended to include most cohorts to maximize the sample size of the summary statistics for constructing PRSs while leaving out sufficient cohorts for each ancestry to be used for training and validation.

Cohorts for the training and validation of the PRSs

We trained the PRSs in one cohort per ancestry group and validated them in at least four validation cohorts per ancestry. All training and validation cohorts included unrelated individuals and were independent of those included in the GWAS summary statistics to avoid overfitting (figure 1B, C, appendix 2 tabs 3-6). Except for the AoU cohort, for which whole genome sequencing is available, the genotyping of the other cohorts was chip array-based. The genotypes were imputed to the 1KG[4] or the TOPMed r2[7,8] reference panels using the Michigan Imputation server.[9] We applied a separate post-imputation quality control in each cohort and ancestry to keep biallelic nonpalindromic SNPs with an imputation quality of r^2≥0·8 and MAF≥0·005. We excluded the variants not included in the LD reference panels, as explained below, or variants that showed an allelic frequency discordance≥0·2 compared to the 1KG ancestry-specific allelic frequency.

LD reference panels for the construction of the PRSs

To account for the correlation between variants, we constructed customized ancestry-specific LD reference panels using the same scripts used in PRS-CS[10] and PRS-CSx[11] tools. We built four new sets of ancestry-specific LD reference panels using the HapMap3 (HM3) set of variants, similar to the official panel (https://github.com/getian107/PRScsx), or an expanded 1KG set of variants, along with pairwise LD from the 1KG or in-house samples.

First, we identified ancestry-specific LD blocks using LDetect.[12] For each of the five ancestry groups in the 1KG dataset (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html#reference), we selected common SNPs with MAF≥0·01 to generate a covariance matrix of variants based on the LD r^2 calculated in PLINK v1·9[13] and derived the boundaries of LD blocks. Second, we generated two sets of reference SNPs. One was based on the HM3 set of variants (https://www.sanger.ac.uk/data/hapmap-3/), similar to the official PRS-CS[10]/PRS-CSx[11] HM3 version. Another expanded set of variants based on 1KG (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html#reference) was selected using the Tag(ging) It(erative) of SNPs in multiple populations (TagIt) program.[14] TagIt allows the selection of tag SNPs by leveraging genetic information from multiple diverse ancestries to maximize cross-population coverage. We only included non-palindromic SNPs with MAF≥0·01 in at least one ancestry group for both the HM3 and TagIt SNP lists. Third, the two sets of SNPs were extracted in each ancestry for individuals from the 1KG dataset (347 to 661 individuals per ancestry) and from the larger imputed in-house datasets (including around 10,000 individuals per ancestry). SNPs with low imputation quality (r^2<0·8) were further excluded in the in-house datasets. Last, we calculated the variants' pairwise LD (r^2) using PLINK v1·9 to generate ancestry-specific LD reference panels. In total, for each ancestry, we built four different LD reference panels and used them to construct the PRSs, combining two sets of variants (i.e., HM3 and TagIt) and two sources of LD information (i.e., 1KG and in-house samples) (appendix 2 tab 7).

Training of the PRSs

We used the PRS-CS[10] Bayesian polygenic method to construct single-ancestry PRSs. For each ancestry group, we leveraged the T2D GWAS summary statistics and LD reference panels matching the ancestry of the validation cohort (e.g., a PRS trained using the AMR GWAS and AMR LD reference panel to be validated in AMR cohorts). When applicable, we also modeled non-matched single-ancestry PRSs (e.g., a PRS trained using the EUR GWAS and EUR LD reference panel to be evaluated in AMR validation cohorts). The PRS-CS method returns a single-ancestry posterior variant effect size.

We then used PRS-CSx[11] to construct multi-ancestry PRSs. Instead of meta-analyzing the ancestry-specific GWAS summary statistics, PRS-CSx jointly models the GWAS summary statistics along with their matching LD reference panels, using a shared continuous shrinkage prior, to generate ancestry-specific variant posterior effect sizes in a coupled manner that leverages cross-population genetic architecture. We used these ancestry-specific effect sizes to compute standardized ancestry-specific z-scores, which were then combined in a linear regression model to derive the multi-ancestry posterior variant effect size as follows:

$$y = PRS_{\theta,AFR} + PRS_{\theta,AMR} + PRS_{\theta,EAS} + PRS_{\theta,EUR} + PRS_{\theta,SAS}$$

Where y is the T2D status, and $PRS_{\theta,\text{ ancestry group}}$ is the standardized PRS for a given shrinkage prior (θ) and ancestry.

For both PRS-CS and PRS-CSx, we used the training cohorts to select the optimal continuous shrinkage prior from five phi values (i.e., 0·01, 0·001, $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$) based on predictive performance. In total, we constructed 80 PRSs for each of the AFR, AMR, and SAS ancestry groups (i.e., 1 matched-ancestry PRS, 2 non-matched ancestry PRSs, and 1 multi-ancestry PRS × 4 LD panels × 5 phi values = 80 models) and 60 PRSs for each of the EAS and EUR ancestry groups (i.e., 1 matched-ancestry PRS, 1 non-matched ancestry PRS, and 1 multi-ancestry PRS × 4 LD panels × 5 phi values = 60 models), resulting in 360 PRS models overall.

To test the predictive performance, we applied the posterior variant effect sizes for each PRS model to calculate the individual scores in each of the five training cohorts using the --score function in PLINK v1·9.[9] We standardized them to have a mean of zero and unit variance. Then, we fitted two logistic regression models and calculated the area under the receiver operator characteristic curve (AUC) using the "pROC" package[15] in R. One model included the explanatory variables sex, age, and genetic PCs, and a second full model also included the standardized PRS. We also fitted logistic regression models adjusted for body mass index (BMI).

We calculated the incremental AUC (iAUC) by subtracting the AUC of the model without the PRS from the AUC of the full model. We defined the best-trained PRS models as those with the continuous shrinkage prior and LD panel that maximized the iAUC. After the training step, we ended up with four best-trained PRS models for the AFR, AMR, and SAS ancestries (i.e., one matched-ancestry PRS, one EUR non-matched ancestry PRS, one EAS non-matched ancestry PRS, and one multi-ancestry PRS), 3 best-trained PRS models for the EUR ancestry (i.e., one single matched-ancestry PRS, one EAS non-matched ancestry PRS, and one multi-ancestry PRS), and 3 best-trained PRS models for the EAS ancestry (i.e., one single matched-ancestry PRS, one EUR non-matched ancestry PRS, and one multi-ancestry PRS) (appendix 2 tab 8).

Validation of the PRSs

To validate each of the 18 best-trained PRSs, we applied the posterior variant effect sizes in a second set of unrelated samples and independent cohorts from each ancestry group. We calculated the individual scores in each validation cohort using the --score function in PLINK 1·9[13] and standardized them to have a mean of zero and unit variance. For the multi-ancestry PRS, we combined ancestry-specific standardized scores weighted for the trained ancestry-specific effect sizes as follows:

$$y = \beta_{\theta,AFR}\, PRS_{\theta,AFR} + \beta_{\theta,AMR}\, PRS_{\theta,AMR} + \beta_{\theta,EAS}\, PRS_{\theta,EAS} + \beta_{\theta,EUR}\, PRS_{\theta,EUR} + \beta_{\theta,SAS}\, PRS_{\theta,SAS}$$

Where y is T2D status, $\beta_{\theta,\text{ ancestry group}}$ is the regression coefficient for a given shrinkage prior and ancestry in the training cohort, and $PRS_{\theta,\text{ ancestry group}}$ is the standardized PRS for a given shrinkage prior and ancestry in the validation cohort.

To test the predictive performance of the PRS, we calculated i) the iAUC as explained above, ii) the proportion of the variation in the T2D status explained by the PRS using Nagelkerke's r^2, iii) the odds ratio per standard deviation (OR per SD) change in the PRS, and iv) the discrimination capacity at the extremes of the PRS distribution by identifying

the individuals at the top 97·5th percentile, 95th percentile and 90th percentile for comparison with the interquartile range.

We applied the DeLong test to statistically assess the difference between iAUCs of the single ancestry vs. multi-ancestry PRSs. We combined the PRS estimates across validation cohorts using fixed-effects meta-analyses by ancestry, weighting each cohort's beta coefficient by the inverse of its variance, using the "metafor" package[16] in R (appendix 2 tab 9,10).

Comparison of the best-performing multi-ancestry PRSs to previously published T2D PRS

Multiple efforts have been made to improve the portability of PRS to apply to individuals from diverse ancestries. Until the preparation of this work (revised on October 07, 2024), 147 PRSs for T2D had been constructed and made publicly available through the PGS catalog.[17] To compare the performance of our best-trained PRS models using PRS-CSx (which we refer to as 'D-PRISM multi-ancestry PRS-CSx' model), we selected 55 PRSs from the PGS catalog that i) were trained for the overall T2D trait and not for any specific subtype of the disease, ii) were trained considering all types of genetic variants and not any specific set of variants for specific biological mechanisms, and iii) were constructed and trained by leveraging genetic information from cohorts other than the AoU, which we used as a validation cohort in this study.

We downloaded the PRSs and extracted the variants from the AoU cohort[18] (release v7, May 2022). Since the variant missingness rate was below 10% for all PRSs, we included all of them for testing. We calculated the individual scores in each of the five ancestries using the --score function in PLINK v1·9[13] and standardized them to mean zero and unit variance. Then, we tested the performance of the PRSs using the same procedure as for the validation cohorts.

To assess the added value of the PRS-CSx approach over constructing a PRS from meta-analyzed multi-ancestry GWAS results, we performed an IVW meta-analysis of D-PRISM ancestry-specific GWAS summary statistics and applied PRS-CS to the resulting meta-analysis. We used the EUR 1KG HM3 LD reference panel and allowed the shrinkage prior to be automatically learned from the data (which we refer to as 'D-PRISM multi-ancestry PRS-CS' model).

Similarly, we also evaluated the performance of a PRS based on the most statistically powered multi-ancestry T2D GWAS to date from Suzuki et al.[19,] including a 16% larger sample size than this study (i.e., Suzuki et al.: 2,535,601 individuals including 428,452 T2D cases and 2,107,149 controls vs. D-PRISM: 2,185,548 individuals including 359,819 T2D cases and 1,825,729 controls). We first applied the same quality control steps as those used for D-PRISM GWAS summary statistics and then used PRS-CS to construct a PRS using the EUR 1KG HM3 LD reference panel and let the prior shrinkage prior to be automatically learned from the data (which we refer to as 'Suzuki et al., PRS-CS' model).

Additionally, we constructed an rsPRS using the 1,289 distinct T2D variants identified by Suzuki et al.,[19] defined as having an association $p<5 \times 10^{-8}$. For 90 out of 203 palindromic variants, we used proxy variants ($r^2 \geq 0{\cdot}8$ in all the ancestry groups). We excluded 113 variants, as no proxy was available, thereby using 1,176 variants to construct the rsPRS (which we refer to as 'Suzuki et al., rsPRS' model) (appendix 2 tab 11).

Association of PRSs with diabetes complications and comorbidities

We also evaluated the association of the best-performing D-PRISM multi-ancestry PRS-CSx models with T2D-related microvascular complications (i.e., diabetic nephropathy, diabetic retinopathy, end-stage diabetic nephropathy, and proliferative diabetic retinopathy) and comorbidities (i.e., cardiovascular disease and ischemic stroke) in individuals with T2D in the AoU validation cohort. To comply with the AoU policies, we only considered individuals of the AFR, AMR, and EUR ancestry groups, as there were limited sample sizes for the EAS and SAS ancestries (i.e., <30 individuals with diabetes complications). We defined the traits based on International Classification of Diseases (ICD) codes (versions 9 and 10), as previously described (appendix 2 tab 12).[19] We tested the association of each T2D-related traits with the standardized PRSs by fitting logistic regression models adjusted for sex, age, and genetics PCs in each ancestry group, separately (appendix 2 tab 13).

The defining ICD codes for microvascular complications were restricted to those explicitly indicating a diabetic etiology. However, to establish the temporal sequence between diabetes and its microvascular complications, we extracted the date when the microvascular ICD code was assigned and contrasted it with an estimated date of diabetes

onset. To estimate the date of diabetes onset, we leveraged the EHR and survey data to extract the earliest date when a patient met altered glycemic criteria (HbA1C≥6.5% or random glucose≥200 mg/dL at outpatient settings), had an ICD code for T2D, or was prescribed a diabetes-specific medication at outpatient settings (insulin or non-insulin). When available, this estimated date was contrasted with the self-reported date of diagnosis. If the estimated onset date fell outside the self-reported diagnosis window, the evidence was considered insufficient to establish a reliable onset time-point. Once we estimated the date of diabetes onset, we considered a post-diabetes complication when the estimated age at diabetes onset preceded the first record of the relevant outcome by 6 months or more. More than 70% of the individuals were recorded to have a microvascular complication after the estimated age at diabetes onset (79% with DR, 77% with PDR, 85% with DN, and 72% with ESDN).

We performed two additional sensitivity analyses. First, we restricted the analysis to T2D patients where the estimated age at T2D onset preceded the first record of the complication. This analysis yielded consistent results compared to the analysis of the overall sample (Supplementary Figure 10). Second, we adjusted for the estimated duration of T2D, in addition to the other covariates, to assess whether the PRS's effect was mediated by T2D duration (e.g., via earlier onset) or if it represented a direct effect independent of duration. T2D duration was defined as: T2D duration = last age in EHR record - EHR-based estimated age at T2D onset. Although the effect was attenuated, the PRS remained significantly associated with complications, suggesting a direct effect risk independent of disease duration (Supplementary Figure 11; appendix 2 tab 13).

Association of PRSs with incident T2D, alone and in combination with clinical risk factors

To better assess the clinical impact of the PRSs, we extracted EHR data from the All of Us v8 cohort, implemented a comprehensive clinical risk score (CRS) based on the T2D Framingham Risk Score[20] and assessed the effects of the PRS in the context of the CRS.

We extracted EHR data from January 1, 2000, to December 31, 2023, and considered patients who had received primary care data and had at least two records with available glucose measurements at outpatient settings. After excluding patients with a T2D diagnosis before or within 1 year of their first record (the "baseline date"), 17,920 individuals with available CRS data remained for the analysis. Of these, 2,074 developed incident T2D and 15,846 remained non-diabetic during follow-up. Only individuals who met criteria for T2D based on a previously reported algorithm for T2D in the All of Us cohort were considered incident cases.[21] Time to T2D onset was defined as the time until a participant met glycemic criteria for T2D (HbA1C ≥6.5% or random glucose at an outpatient setting ≥ 200 mg/dL), had an ICD code for T2D, or was prescribed a diabetes-specific medication (insulin or non-insulin) at an outpatient setting during the observation period. Individuals were right-censored at the date of the first T2D-defining event or their last clinical record before December 31, 2023.

For this cohort, we implemented an adapted clinical risk score (CRS) based on the Framingham Offspring Study as described in Mandla et al.[22] This CRS comprised 9 components: age, sex, parental history of T2D, body mass index (BMI), systolic blood pressure (SBP), high-density lipoprotein (HDL), total cholesterol, triglycerides, and random glucose. The original Framingham score included fasting glucose and waist circumference, but these were not available in AoU data. Therefore, we omitted waist circumference and used random glucose values as a proxy for fasting glucose. Briefly, for each participant, we extracted the mean values of SBP, HDL, total cholesterol, triglycerides, and random glucose measurements at the outpatient setting between 1 year before and 1 year after their baseline date. No imputation of missing data was performed. The parental history of T2D was extracted from survey data, and we used the median BMI during the follow-up period. The resulting CRS was log-transformed to be normally distributed and standardized.

We evaluated the predictive value of the PRS for T2D across the three ancestries for which we had sufficient sample size: AFR, AMR, and EUR. We performed Kaplan-Meier survival analysis, stratifying participants by tertiles of the PRS. To quantify this risk, Cox proportional hazards models were fitted for each ancestry group. We next investigated whether the PRS provided predictive value independent of random glucose, a primary T2D risk factor. We stratified participants into those with random glucose < 140 mg/dl (i.e., normoglycemia), and those with random glucose ≥140 mg/dl (i.e., one of the criteria to define prediabetes) and compared the effects of each PRS tertile in each group. To formally quantify this combined effect, we fitted Cox models setting the group with the lowest PRS tertile (T1) and random glucose <140 mg/dl as reference. Finally, we also evaluated the added value of the PRS in addition to the CRS. We then fitted a multivariable Cox model including the PRS, the CRS, and genetic principal components. All

models were adjusted for the genetic principal components. Median follow-up time was estimated using the reverse Kaplan-Meier method.

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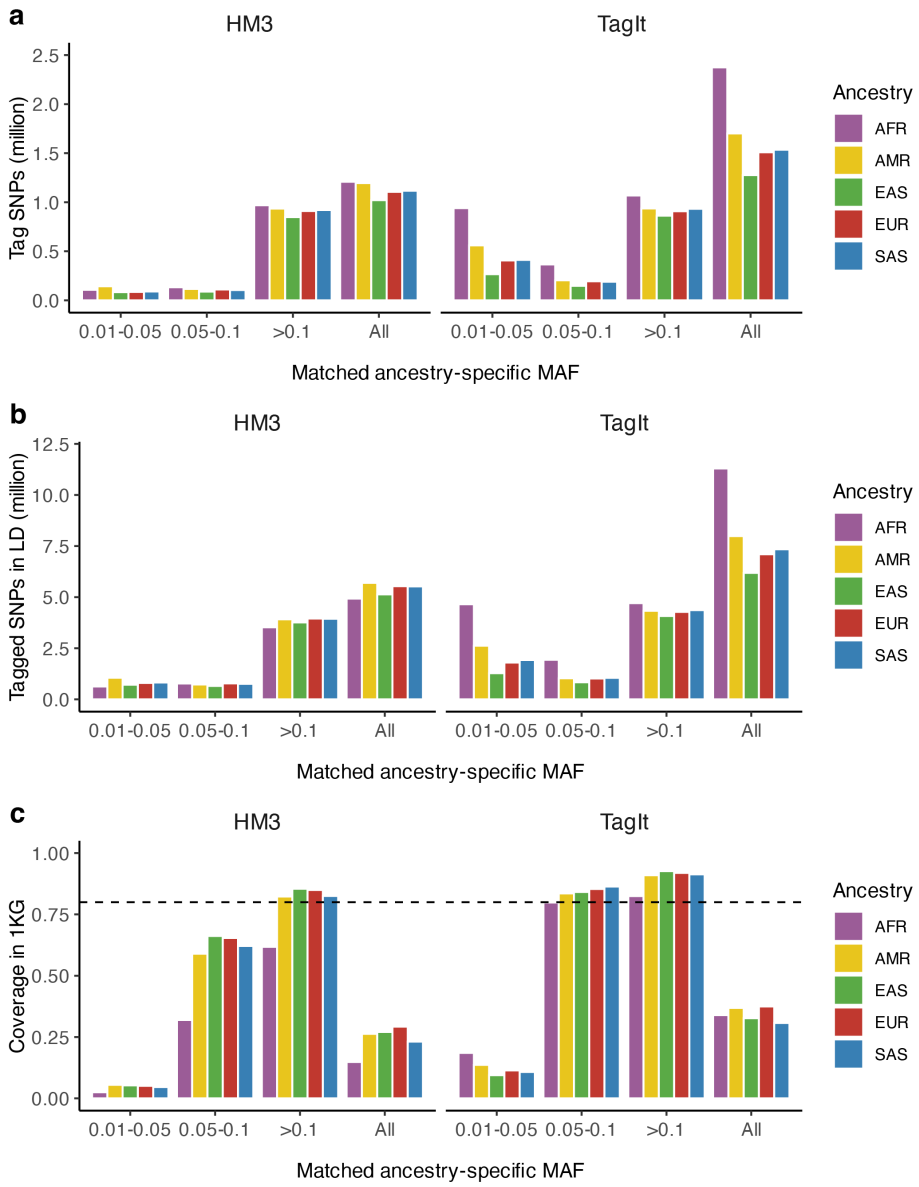
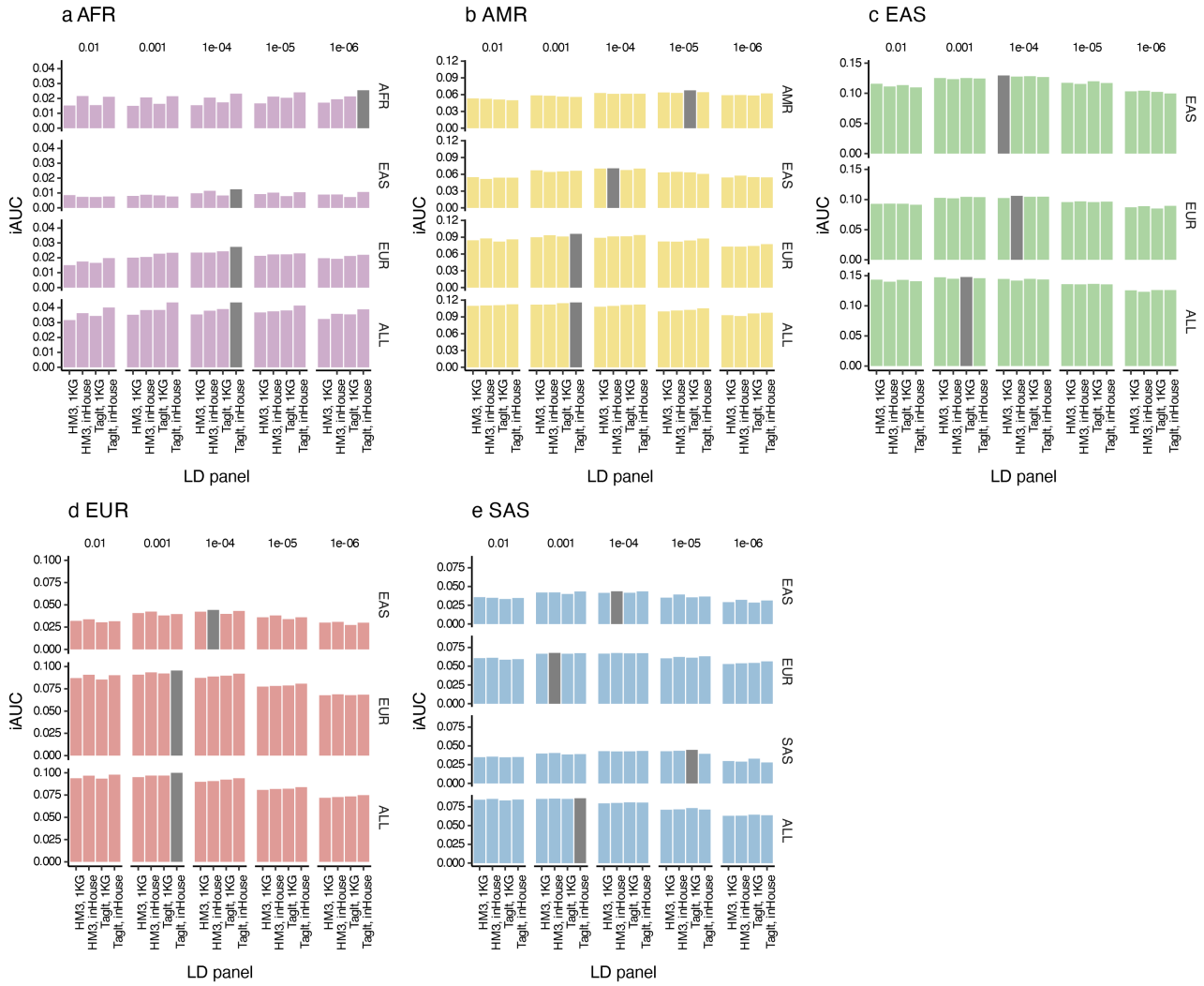
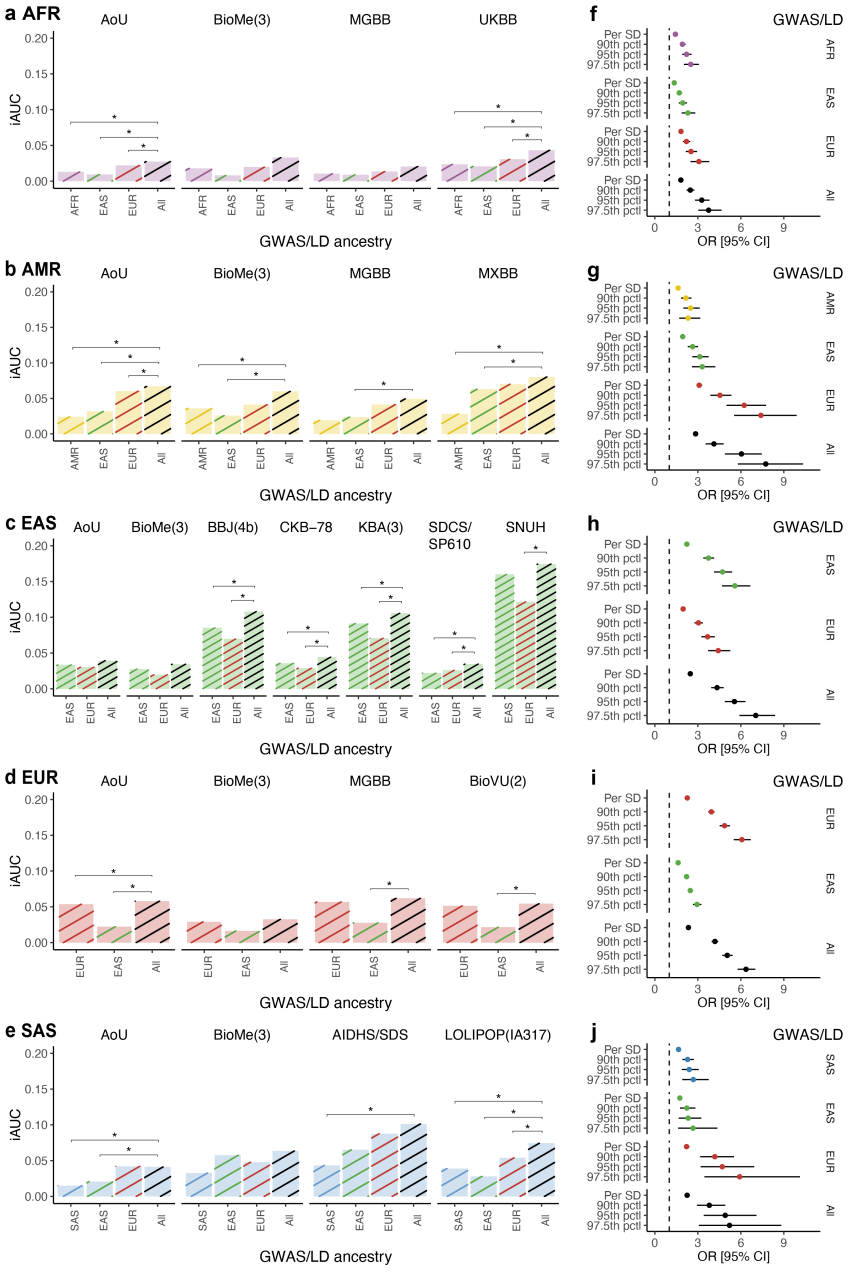
Supplementary Figures



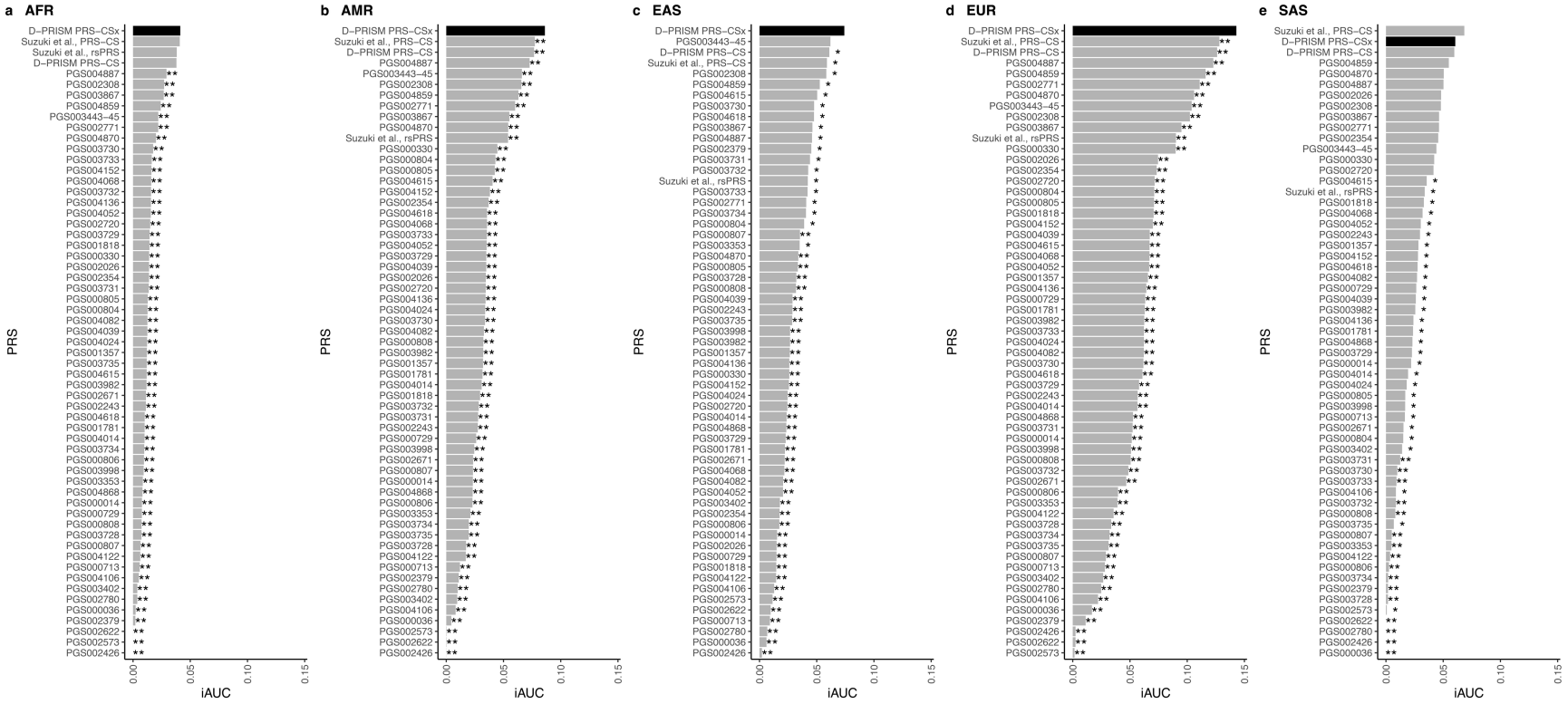
Supplementary Figure 1 | Tag SNPs informativeness across ancestries. We considered two sets of reference SNPs: one was based on the HapMap3 (HM3) set of variants, and the other was selected using the TagIt program. **a,** Number of tag SNPs in the LD reference panels, stratified by minor allele frequency and ancestry (*left*, HM3-based; *right*, TagIt-based), **b,** Number of SNPs being tagged in the LD reference panels, stratified by minor allele frequency and ancestry for a minimum pairwise correlation threshold of r^2>0.8 (*left*, HM3-based; *right*, TagIt-based), **c,** Proportion of SNPs that are either tags or are tagged (r^2>0.8) in the LD reference panels, stratified by minor allele frequency and ancestry in the individuals from 1KG. The dashed line represents 80% coverage.



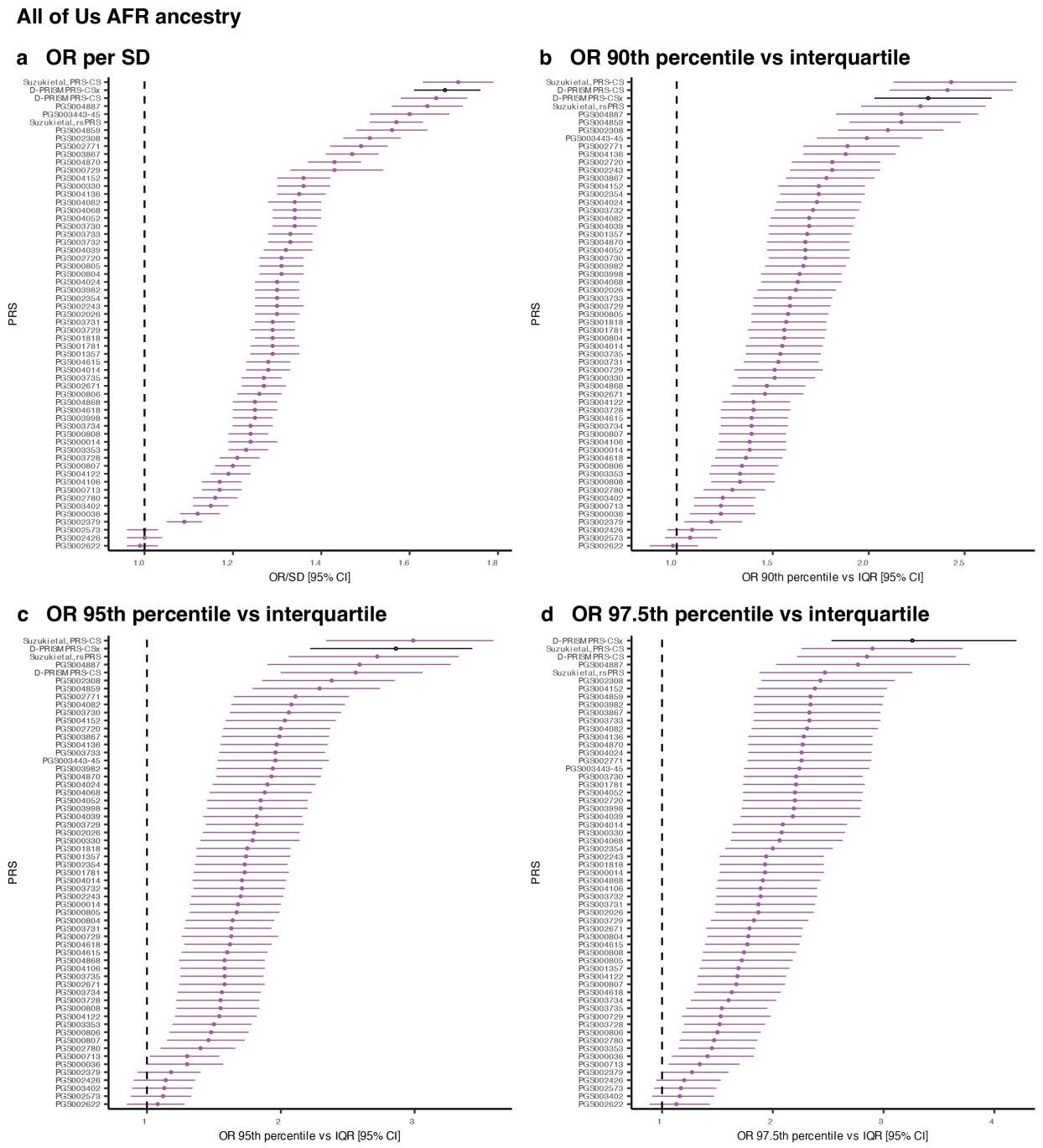
Supplementary Figure 2 | Performance of the T2D PRSs in the training cohorts across ancestry groups. Incremental AUC (iAUC) of the T2D PRS in the training cohorts: **a**, AFR, **b,** AMR, **c,** EAS, **d,** EUR, **e,** SAS. For each ancestry, we trained single-ancestry and multi-ancestry (ALL) PRSs using four LD panels and 5 phi continuous shrinkage priors. Bar colors represent the ancestry group: purple for AFR, yellow for AMR, green for EAS, red for EUR, and blue for SAS. The grey color highlights the best-trained PRS models that maximize the iAUC. All models were adjusted for sex, age, and genetic principal components.



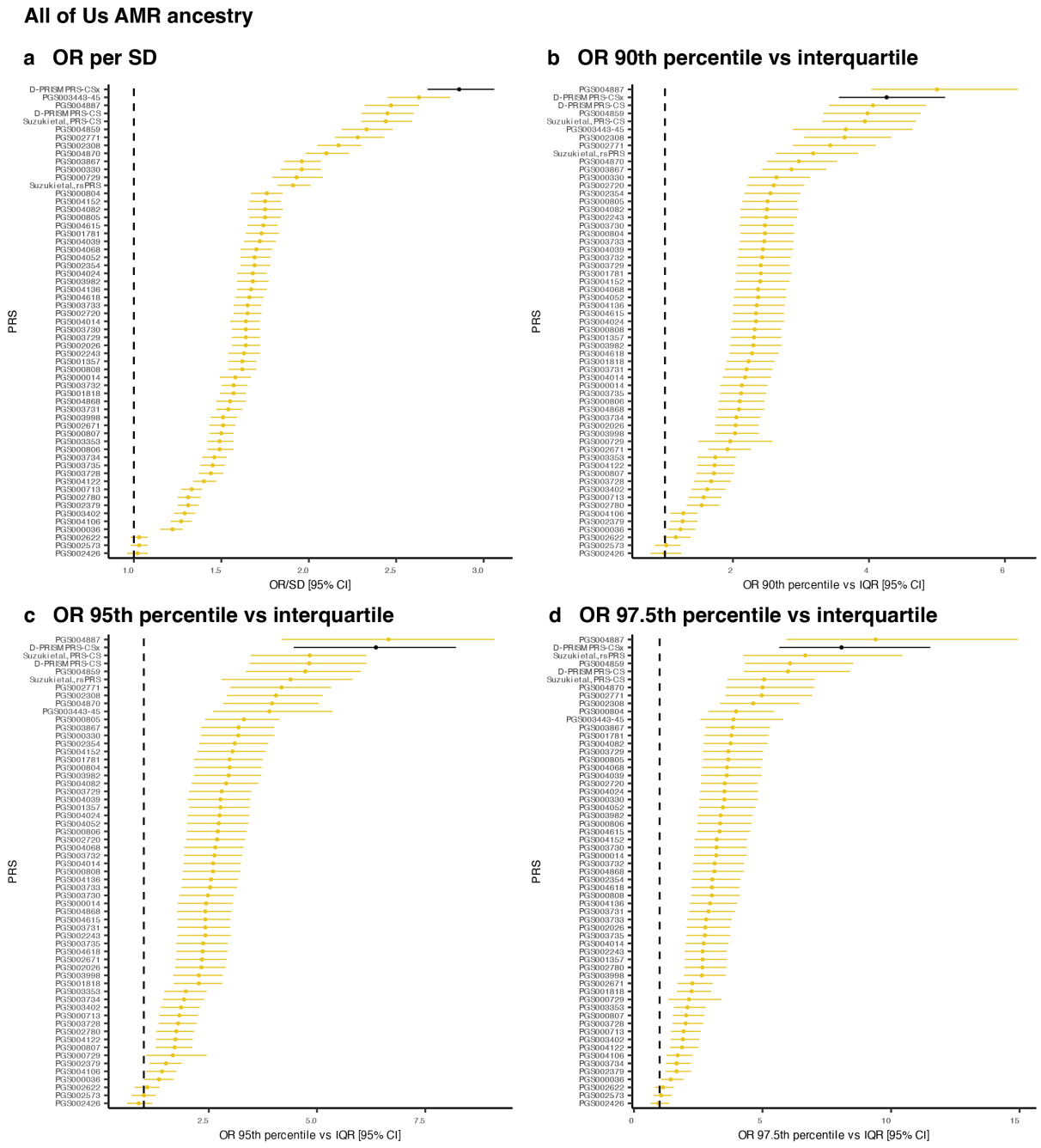
Supplementary Figure 3 | Performance of the T2D PRSs adjusted for BMI in the validation cohorts across ancestry groups. a-e: Incremental AUC (iAUC) of the T2D PRS in the validation cohorts across ancestry groups: **a,** AFR, **b,** AMR, **c,** EAS, **d,** EUR, **e,** SAS. For each ancestry, the best-performing single-ancestry and multi-ancestry (All) PRSs were evaluated. Each bar represents a single cohort. Bar colors represent the ancestry group: purple for AFR, yellow for AMR, green for EAS, red for EUR, and blue for SAS. Line colors represent the ancestry of the T2D GWAS summary statistics and LD panels used to train the PRS, using the same color codes for single-ancestry PRSs, and black for multi-ancestry PRSs. **f-j:** Odds ratio (OR) from the meta-analysis of validation cohorts across ancestry groups: **f,** AFR, **g,** AMR, **h,** EAS, **i,** EUR, **j,** SAS. Points represent the odds ratio per standard deviation of the PRS distribution or the odds ratio comparing different PRS distribution extremes relative to the interquartile range. Error bars show the 95% confidence intervals (95% CI). Point colors represent the ancestry of the T2D GWAS summary statistics and LD panels used to train the PRS. * De Long $p<0.05$. All models were adjusted for sex, age, and genetic principal components



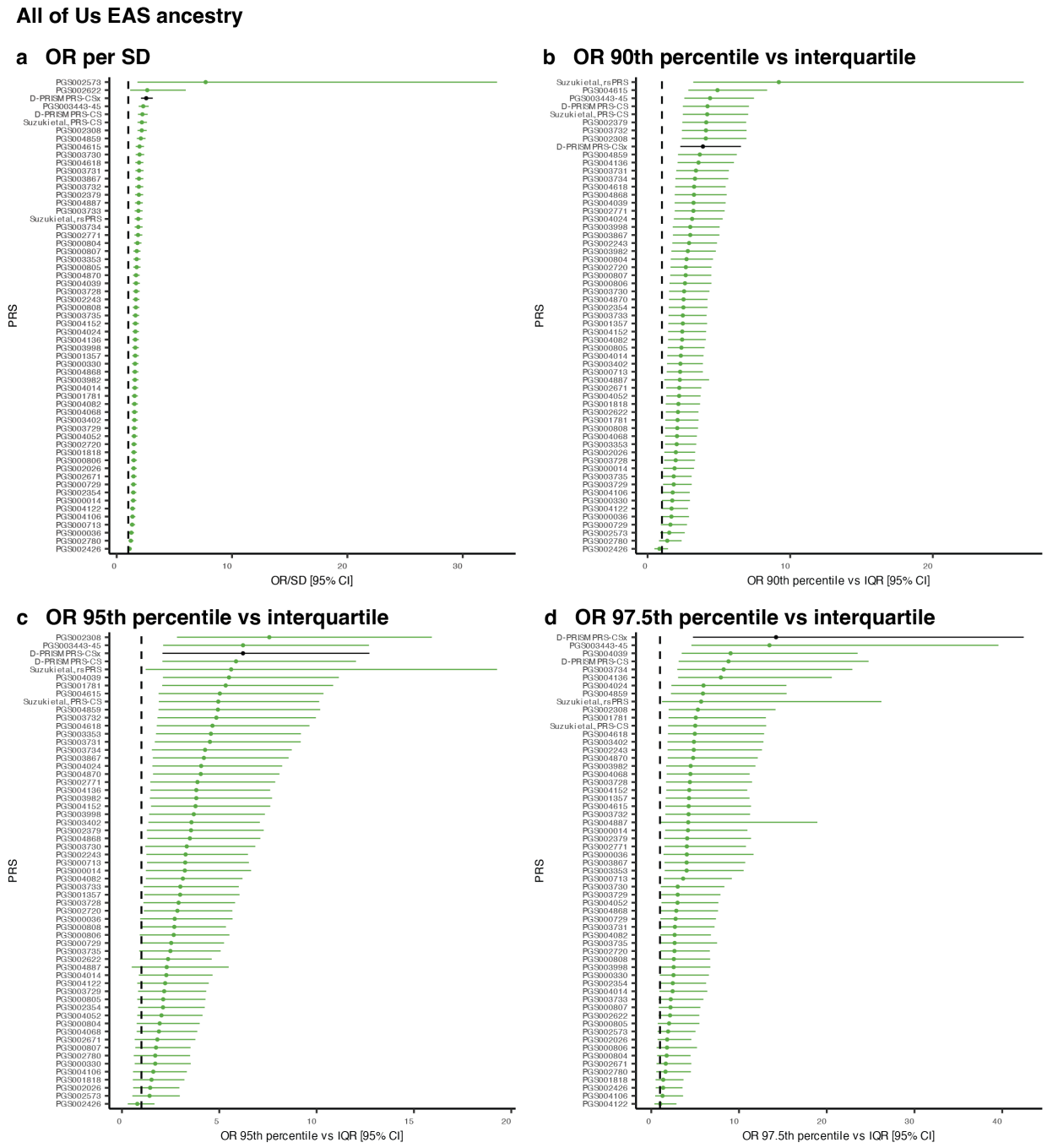
Supplementary Figure 4 | Performance of D-PRISM multi-ancestry PRSs compared to published T2D PRSs from the PGS Catalog and other sources in the All of Us cohort. a-e: Incremental AUC (iAUC) across ancestry groups: **a,** AFR, **b,** AMR, **c,** EAS, **d,** EUR, **e,** SAS. Black bars highlight this study's multi-ancestry PRSs. *DeLong $p<0.05$; **Bonferroni-corrected DeLong $p<9\times10^{-4}$. All models were adjusted for sex, age, and genetic principal components.



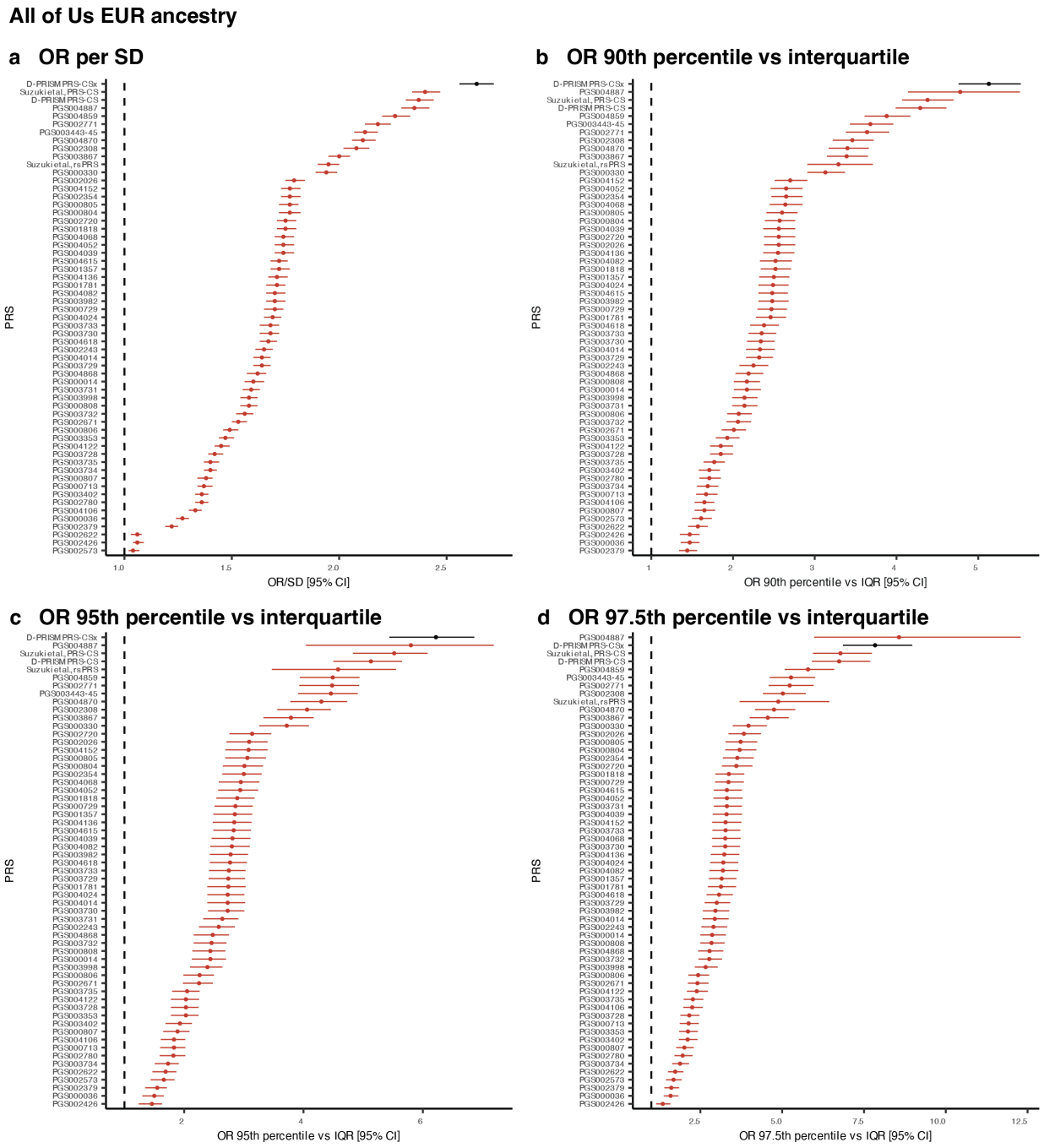
Supplementary Figure 5 | Performance of D-PRISM multi-ancestry PRS-CSx compared to the published T2D PRSs from the PGS Catalog and others in individuals of AFR ancestry from the All of Us validation cohort. a, Odds ratio per standard deviation (OR per SD) of the PRS distribution, **b,** OR comparing the 90th percentile of the PRS relative to the interquartile range, **c,** OR comparing the 95th percentile of the PRS relative to the interquartile range, **d,** OR comparing the 97.5th percentile of the PRS relative to the interquartile range. All models were adjusted for sex, age, and genetic principal components.



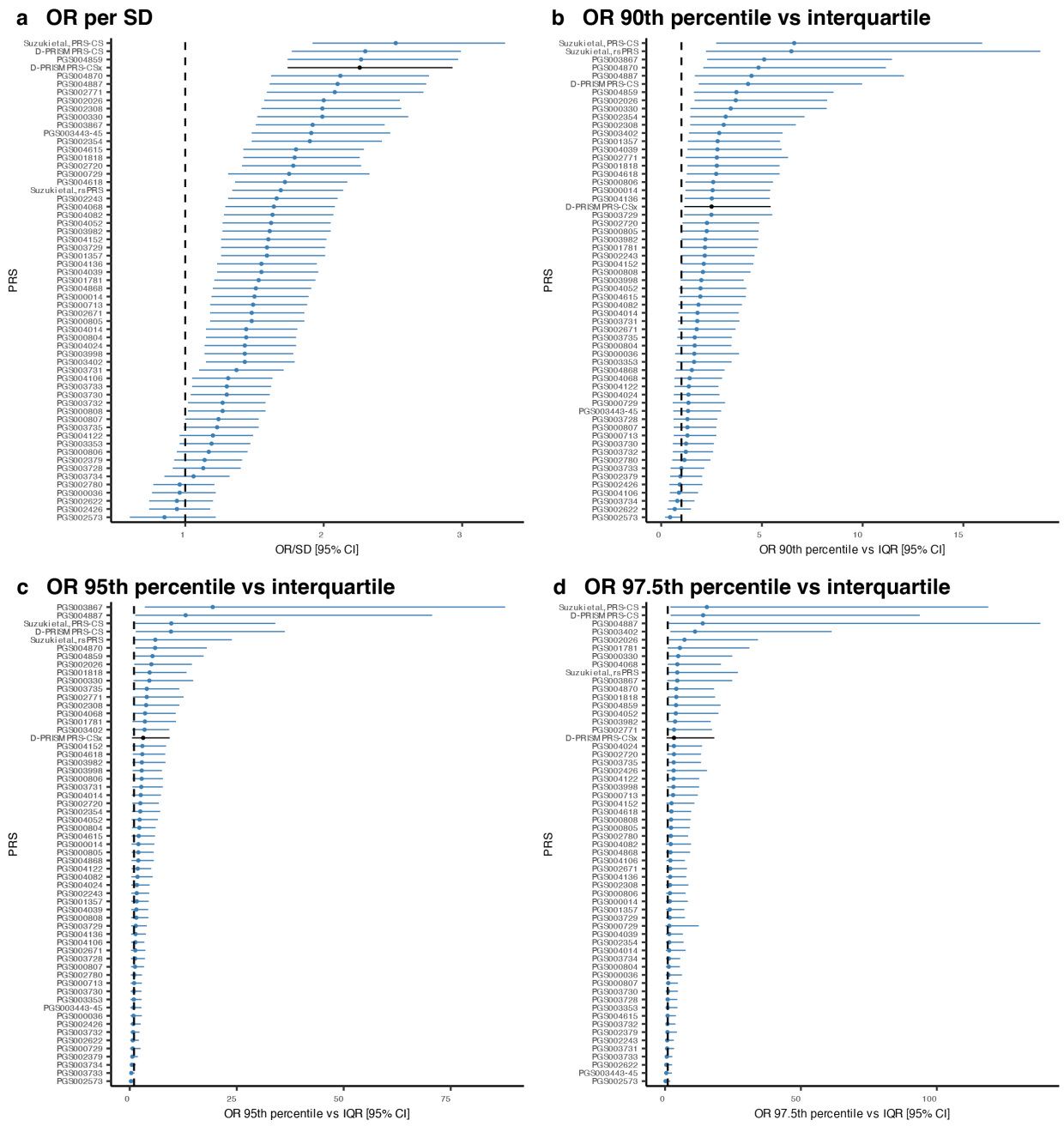
Supplementary Figure 6 | Performance of D-PRISM multi-ancestry PRS-CSx compared to the published T2D PRSs from the PGS Catalog and others in individuals of AMR ancestry from the All of Us validation cohort. a, Odds ratio per standard deviation (OR per SD) of the PRS distribution, **b,** OR comparing the 90th percentile of the PRS relative to the interquartile range, **c,** OR comparing the 95th percentile of the PRS relative to the interquartile range, **d,** OR comparing the 97.5th percentile of the PRS relative to the interquartile range. All models were adjusted for sex, age, and genetic principal components.



Supplementary Figure 7 | Performance of D-PRISM multi-ancestry PRS-CSx compared to the published T2D PRSs from the PGS Catalog and others in individuals of EAS ancestry from the All of Us validation cohort. a, Odds ratio per standard deviation (OR per SD) of the PRS distribution, **b,** OR comparing the 90th percentile of the PRS relative to the interquartile range, **c,** OR comparing the 95th percentile of the PRS relative to the interquartile range, **d,** OR comparing the 97.5th percentile of the PRS relative to the interquartile range. All models were adjusted for sex, age, and genetic principal components.

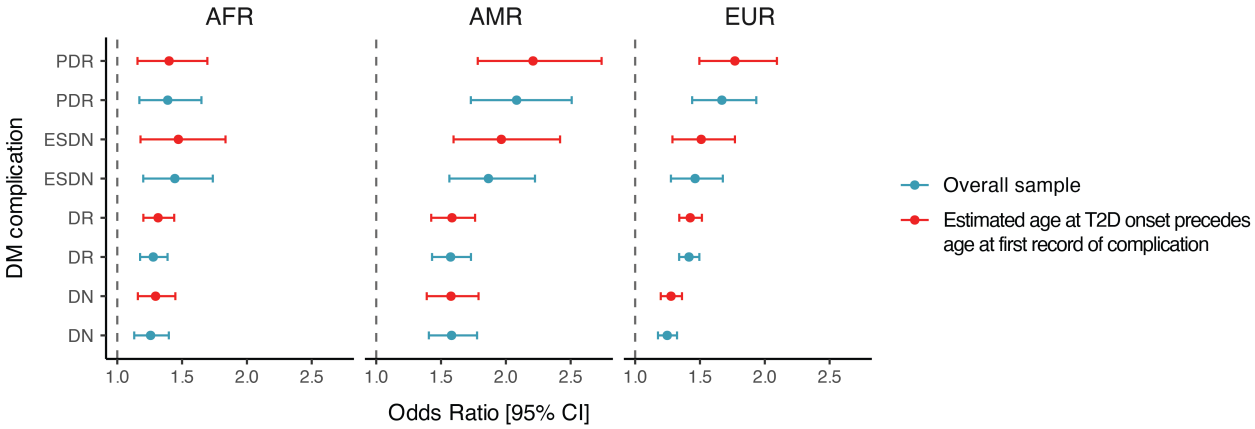


Supplementary Figure 8 | Performance of D-PRISM multi-ancestry PRS-CSx compared to the published T2D PRSs from the PGS Catalog and others in individuals of EUR ancestry from the All of Us validation cohort. a, Odds ratio per standard deviation (OR per SD) of the PRS distribution, **b,** OR comparing the 90th percentile of the PRS relative to the interquartile range, **c,** OR comparing the 95th percentile of the PRS relative to the interquartile range, **d,** OR comparing the 97.5th percentile of the PRS relative to the interquartile range. All models were adjusted for sex, age, and genetic principal components.

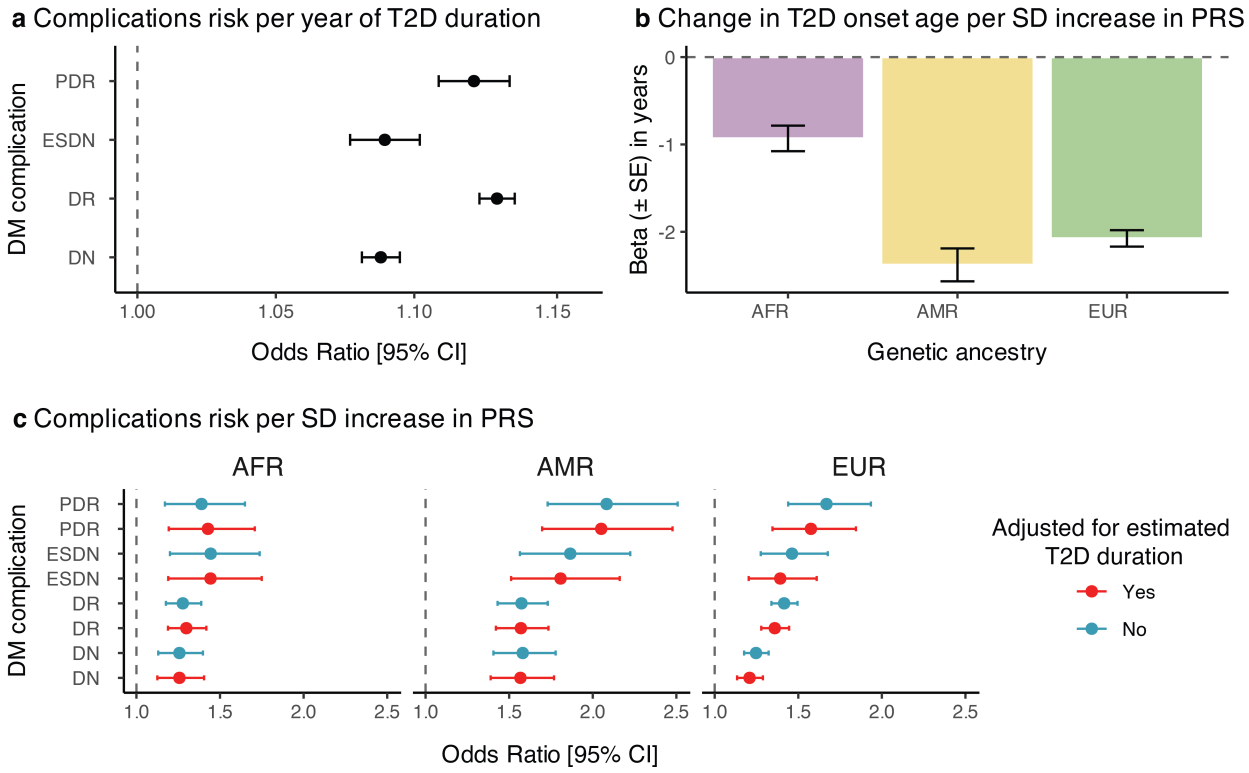


Supplementary Figure 9 | Performance of D-PRISM multi-ancestry PRS-CSx compared to the published T2D PRSs from the PGS Catalog and others in individuals of SAS ancestry from the All of Us validation cohort. a, Odds ratio per standard deviation (OR per SD) of the PRS distribution, **b,** OR comparing the 90th percentile of the PRS relative to the interquartile range, **c,** OR comparing the 95th percentile of the PRS relative to the interquartile range, **d,** OR comparing the 97.5th percentile of the PRS relative to the interquartile range. All models were adjusted for sex, age, and genetic principal components.

Temporal sequence of estimated age at diabetes onset and first record of the microvascular complication based on the All of Us v8 EHR and survey data.				
	% of T2D cases with microvascular complications			
	PDR	ESDN	DR	DN
Estimated age at T2D onset precedes age at first record of complication	77%	72%	79%	85%
Age at first record of complication precedes estimated age at T2D onset	18%	22%	14%	7%
Unavailable estimated age at T2D onset	5%	6%	7%	8%



Supplementary Figure 10 | Sensitivity analysis of the association of D-PRISM Multi-Ancestry Polygenic Risk Score (PRS) with Diabetes Microvascular Complications in the All of Us Research Program Cohort. The plot displays the Odds Ratio (OR) per standard deviation increase in the D-PRISM PRS for four outcomes: proliferative diabetic retinopathy (PDR), end-stage diabetic nephropathy (ESDN), diabetic retinopathy (DR), and diabetic neuropathy (DN). Points are colored to indicate the sample used: red for individuals for whom the estimated diabetes onset preceded the complication EHR first record, and blue for the overall sample. Error bars indicate the 95% confidence intervals (95% CI). All models were adjusted for sex, age, and genetic principal components.



Supplementary Figure 11 | Effect of PRS and T2D duration on risk of microvascular complications. a, Odds Ratio per year of EHR-based estimated T2D duration for Proliferative Diabetic Retinopathy (PDR), End-Stage Diabetic Nephropathy (ESDN), Diabetic Retinopathy (DR), and Diabetic Nephropathy (DN). The plot shows a significant positive association between microvascular complications and T2D duration, with up to a 1.12-fold increased risk per year. All models were restricted to T2D cases and adjusted for sex and genetic principal components. **b,** Change in T2D onset age (years) per one-SD increase in PRS, stratified by genetic ancestry. One-SD increase in the T2D PRS was associated with up to 2.3 years earlier onset of T2D across genetic ancestries. Models were adjusted for sex and genetic principal components. Bars represent the beta coefficient (change in years), and error bars show the 95% confidence intervals (95% CI). **c,** Odds Ratio per one-SD increase in PRS for PDR, ESDN, DR, and DN. All models were adjusted for sex, age, and genetic principal components. Points are colored based on statistical adjustment for T2D duration: red (adjusted for T2D duration) and blue (unadjusted).

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Singapore Chinese Eye Study (SCES) is supported by the National Medical Research Council (NMRC), Singapore (grants 0796/2003, 1176/2008, 1149/2008, STaR/0003/2008, 1249/2010, CG/SERI/2010, CIRG/1371/2013, and CIRG/1417/2015), and Biomedical Research Council (BMRC), Singapore (08/1/35/19/550 and 09/1/35/19/616).

Starr County Health (SCH) was supported by grants from the National Institutes of Health (DK073541, DK085501, HL102830 and DK116378) and funds from the State of Texas. SCH thank the field staff in Starr County for their careful collection of these data and are especially grateful to the participants who so graciously cooperated and gave of their time. Starr County Health Singapore Chinese Health Study (SCHS) was supported by the US National Institutes of Health grants R01DK08072, R01CA144034 and UM1CA182876.

Slim Initiative for Genomic Medicine in the Americas (SIGMA). This work was conducted as part of the Slim Initiative for Genomic Medicine, a joint U.S.-Mexico project funded by the Carlos Slim Health Institute. The UNAM/INCMNSZ diabetes study was supported by Consejo Nacional de Ciencia y Tecnología grants 138826, 128877, CONACyT- SALUD 2009-01-115250, and a grant from Dirección General de Asuntos del Personal Académico, UNAM, IT 214711. The Diabetes in Mexico Study was supported by Consejo Nacional de Ciencia y Tecnología grant 86867 and by Instituto Carlos Slim de la Salud, A.C. The Mexico City Diabetes Study was supported by National Institutes of Health (NIH) grant R01HL24799 and by the Consejo Nacional de Ciencia y Tenologia grants: 2092, M9303, F677-M9407, 251M, and 2005-C01-14502, SALUD 2010-2-151165. The Multiethnic Cohort was supported by NIH grants CA164973, CA054281, and CA063464.

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Samsung Medical Center (SMC) was supported by a grant from Samsung Biomedical Research Institute. Genotyping of the patients and control subjects from SMC was conducted by Duk-Hwan Kim in the Dept. of Molecular Cell Biology, Sungkyunkwan University School of Medicine, and was supported by a grant from Samsung Biomedical Research Institute.

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Danish T2D Case-Control Study (UCPH) was undertaken by the Novo Nordisk Foundation Center for Basic Metabolic Research, which is an independent Research Center, based at the University of Copenhagen, Denmark and partially funded by an unconditional donation from the Novo Nordisk Foundation (www.cbmr.ku.dk, Grant number NNF18CC0034900). Included study samples were supported by the Danish Research Fund and the National Danish Research Fund (The Vejle Diabetes Biobank), the Velux Foundation, The Danish Medical Research Council and Danish Agency for Science, Technology and Innovation (Health 2006); the Danish Research Council, the Danish Centre for Health Technology Assessment and Novo Nordisk Inc. (Inter99), the Timber Merchant Vilhelm Bang's Foundation and the Danish Heart Foundation (Health 2008), TrygFonden, the Lundbeck Foundation and the Novo Nordisk Foundation (NNF15OC0015896, DanFunD).

UK Biobank (UKBB) analyses were conducted using the UK Biobank resource under applications 236, 9161, and 10035. This research was supported by the British Heart Foundation (grant SP/13/2/30111). Large-scale comprehensive genotyping of UK Biobank for cardiometabolic traits and diseases: UK CardioMetabolic Consortium (UKCMC).

Uppsala Longitudinal Study of Adult Men (ULSAM) was supported by Wellcome Trust Grants (WT098017, WT064890, WT090532), Uppsala University, Uppsala University Hospital, the Swedish Research Council, and the Swedish Heart-Lung Foundation.

Wake Forest School of Medicine (WFSM) was supported by NIH grants K99 DK081350, R01 DK066358, R01 DK053591, R01 DK087914, U01 DK105556, R01 HL56266, R01 DK070941 and in part by the General Clinical Research Center of the Wake Forest School of Medicine grant M01 RR07122. Genotyping services were provided by the Center for Inherited Disease Research (CIDR), which is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSC268200782096C.

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Wellcome Trust Case Control Consortium (WTCCC) analysis and genotyping was supported by: Wellcome Trust funding 090367, 098381, 090532, 083948, 085475, 101630, and 203141; MRC (G0601261); EU (Framework 7) HEALTH-F4-2007-201413; and NIDDK DK098032 and U01-DK105535.

Ethics approval committees/IRBs

Anti-aging study cohort (AASC). The ethics committees of Ehime University Graduate School of Medicine approved all study procedures. Written informed consent was obtained from all participants.

All Of Us Research Program (AOURP). All research was conducted under the guidelines defined by the All of Us Ethical Conduct of Research Policy.

Atherosclerosis Risk in Communities (ARIC). Institutional Review Board approvals were obtained at all study sites: National Heart, Lung, and Blood Institute, University of North Carolina at Chapel Hill, Wake Forest Baptist Medical Center, University of Mississippi Medical Center, University of Minnesota, and Johns Hopkins University. All participants provided written informed consent.

Biobank Japan (BBJ). All participants provided written informed consent as approved by the ethical committees of the RIKEN Yokohama Institute and the Institute of Medical Science, the University of Tokyo. Ethical approvals of AMED GRIFIN Diabetes Initiative Japan were gained from the Ethics Committees of Osaka University and the University of Tokyo.

Beijing Eye Study (BES). Approval was obtained from the Medical Ethics Committee of the Beijing Tongren Hospital. All participants gave written informed consent.

BioMe Biobank (BIOME). Approval was obtained from the Institutional Review Board at the Icahn School of Medicine at Mount Sinai. All participants provided written informed consent for genomic data sharing.

Vanderbilt University Medical Center's BioVU (BIOVU). Analyses of DIAMANTE data at Vanderbilt University Medical Center are approved under IRB #190891 and analysis of BioVU data are approved under IRBs #210163 and #171279. In all three cases, the data analyzed received non-human subject determinations.

Bangladesh Population Cohort (BPC). The conduct of the BPC was reviewed and approved by Ethical Committees of the Bangladesh Medical Research Council and Institutional Review Boards of the University of Chicago.

Cardiometabolic Genome Epidemiology (CAGE-AMAGASKI and CAKE-GWAS). Approval was obtained from the Institutional Review Boards at the National Center for Global Health and Medicine. All participants provided written informed consent.

Cardiometabolic Genome Epidemiology (CAGE-KING). Approval was obtained from the ethics committees of Aichi Gakuin University, Jichi Medical University, Nagoya University and Kyushu University. All participants provided written informed consent.

Coronary Artery Risk Development in Young Adults (CARDIA). Participating centers (Northwestern University, University of Alabama Birmingham, University of Minnesota, and Kaiser Foundation Research Institute) provided ethics approval for the CARDIA study, and all participants provided written informed consent to participate.

Cleveland Family Study (CFS). Approval was obtained from the Institutional Review Board of Mass General Brigham (formerly Partners HealthCare). Written informed consent was obtained from all participants.

China Health and Nutrition Survey (CHNS). Approval was obtained from the Institutional review Boards at the University of North Carolina at Chapel Hill, the Chinese National Human Genome Center at Shanghai, and the Institute of Nutrition and Food Safety at the China Centers for Disease Control. All participants provided written informed consent.

Cardiovascular Health Study (CHS). Approval was obtained from the Institutional Review Boards at Wake Forest University, University of California, Davis, Johns Hopkins, University of Pittsburgh, and the University of Washington, Seattle. All participants provided written informed consent.

China Kadoorie Biobank (CKB). All participants provided written informed consent. Ethical approval was obtained from Oxford Tropical Research Ethics Committee (OxTREC) and from the Ethical Review Committees of the Chinese Centre for Disease Control and Prevention and the Chinese Academy of Medical Sciences/Peking Union Medical College.

Cebu Longitudinal Health and Nutrition Survey (CLHNS). Written informed consent was obtained from all participants. Study protocols were approved by the University of North Carolina Institutional review Board for the Protection of Human Subjects.

Diabetic Cohort and Singapore Prospective Study Program (DC/SP2). Study protocols were approved by the Singapore General Hospital Ethics Committee, and National University of Singapore Institutional Review Board. All participants provided written informed consent.

Durban Diabetes Study and Durban Diabetes Case Control (DDS/DCC). Approvals were granted by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal and the UK National Research Ethics Service. All participants provided written informed consent.

deCODE genetics (DECODE). The study was approved by the Icelandic National Bioethics Committee (approval no. VSN-16-112) after evaluation by the Icelandic Data Protection Authority. We obtained written informed consent for all participants in this study who donated samples. All data processing complies with the Icelandic Data Protection Authority (no. PV_2017060950ÞS).

Diabetes Gene Discovery Group (DGDG). All participants signed informed consent, and the protocol was approved by the French ethics committee.

Diabetes Genetics Initiative (DGI). The study was approved by the Ethics Committees of the Helsinki University Hospital, Helsinki, Finland, and Lund University, Sweden.Estonian Genome Center of the University of Tartu (EGCUT). All analyses were approved by the Ethics Review Committee of the University of Tartu. All participants provided written informed consent.

Electronic Medical Records and Genomics Network (EMERGE). Approval was obtained from the Institutional Review Boards at Boston Children's Hospital, Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Essentia Institute of Rural Health, Geisinger Clinic, Group Health Cooperative, Marshfield Clinic Research Foundation, Mayo Clinic, Icahn School of Medicine at Mount Sinai, Northwestern University, Pennsylvania State University, Vanderbilt University Medical Center, and University of Washington. All participants provided written informed consent.

European Prospective Investigation into Cancer and Nutrition (EPIC-INTERACT). The EPIC-InterAct study was approved by the local ethics committee in the participating countries and the Internal Review Board of the International Agency for Research on Cancer. All participants gave written informed consent. The study was coordinated by the Medical Research Council Epidemiology Unit at the University of Cambridge.

Epidemiologic Study of the Screenees for Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (EPIDREAM). All study participants consented to analysis of blood samples. Approval was granted by the Hamilton Integrated Research Ethics Board, at McMaster University, Hamilton, Canada.

Family Heart Study (FAMHS). Approval was obtained from the Institutional Review Board at Washington University, St. Louis. Written informed consent, including consent to participate in genetic studies, was obtained from all participants.

Framingham Heart Study (FHS). Approval was obtained from the Institutional review Board of Boston University Medical Campus. All study participants provided written informed consent.

Finland-United States Investigation of NIDDM Genetics (FUSION). Approval was obtained from the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants provided written informed consent.

German Chronic Kidney Disease (GCKD). All participants provided written informed consent. The study was registered in the national registry for clinical studies (DRKS 00003971) and was approved by local ethics committees.

Genetic Study of Atherosclerosis Risk (GENESTAR). Approval was obtained from the Johns Hopkins Medicine Institutional Review Board. All participants gave written informed consent.

Genetic Epidemiology Network of Arteriosclerosis (GENOA). Approval was granted by Institutional Review Boards of the University of Michigan, University of Mississippi Medical Center and Mayo Clinic. Written informed consent was obtained from all participants.

Resource for Genetic Epidemiology on Adult Heath and Aging (GERA). The Institutional Review Boards for Human Subjects Research of both Kaiser Permanente Medical Care Plan (Northern California Region) and the University of California at San Francisco approved the project.

Genetics of Diabetes and Audit Research in Tayside Scotland (GODARTS). Approval was obtained from the Tayside Medical Ethics Committee. Informed consent was obtained for all participants.

Genetics of Latinos Diabetic Retinopathy (GOLDR). Approval was granted by the Institutional Review Board of the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center.

Genetic Overlap Between Metabolic and Psychiatric Traits and Teens of Attica: Genes and Environment (GOMAP-TEENAGE). Ethical permission for TEENAGE was obtained from the Bioethics Committee of Harokopio University, Athens. Ethical permission for GOMAP was obtained from the Dromokaiteio Scientific Committee, Dromokaiteio Management Committee, Dafni Scientific Committee, Eginitio Scientific Committee and Harokopio Ethics Committee. All participants of GOMAP-TEENAGE gave written informed consent.

Genomic Research Cohort for CCMB Diabetes Study (GRCCDS). Ethics committees of CSIR-Centre for Cellular and Molecular Biology and KEM Hospital and Research Centre approved the project.

Health, Aging and Body Composition Study (HABC). The Institutional Review Boards at the University of Memphis and the University of Pittsburgh granted approval to conduct the Health ABC Study, and all participants provided written informed consent.

Healthy Aging in Neighborhoods of Diversity Across the Life Span Study (HANDLS). Approval was granted by the National Institutes of Health Institutional Review Board (study number 09AGN248). All participants provided written informed consent.

Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Approval was obtained from Institutional Review Boards at the University of North Carolina at Chapel Hill, Albert Einstein College of Medicine, University of Illinois at Chicago, University of Miami, and San Diego State University. All participants provided written informed consent.

Health Professionals' Follow-Up Study (HPFS). Approval was obtained from the Human Research Committee at the Brigham and Women's Hospital. All participants provided written informed consent.

Mexican American Hypertension and Insulin Resistance (HTNIR). Approval was granted by Human Subjects Protection Institutional Review Boards at the University of California at LosAngeles, University of Southern California, Lundquist/LABioMed/Harbor-UCLA and Cedars-Sinai Medical Center.

Howard University Family Study (HUFS). All human participants from the HUFS included in the analyses of this manuscript provided written informed consent prior to enrollment. The HUFS study was approved by the Institutional Review Board at Howard University.

INTERHEART (INTERHEART). All study participants consented to analysis of blood samples. Approval was granted by the Hamilton Integrated Research Ethics Board, at McMaster University, Hamilton, Canada.

Jackson Heart Study (JHS). Approval was obtained from Institutional Review Boards at Jackson State University, Tougaloo College and the University of Mississippi Medical Center. All participants provided written informed consent.

Korean Association Resource (KARE). Approval was granted by the Institutional review Board at the Korean National Institute of Health. All participants provided written informed consent.

Korean Biobank Array from the Korean Genome and Epidemiology (KoGES) Consortium (KBA). Approval was granted by the Institutional Review Board of the Korean National Institute of Health. All participants provided written informed consent.

Collaborative Health Research in the Region of Augsburg (KORA). Approval was granted by the Ethics Committee of the Medical Association of Bavaria (number 06068). All participants provided informed consent.

Los Angeles Latino Eye Study (LALES). Approval was obtained from the Los Angeles County/University of Southern California Institutional Review Board, and Western Institutional Review Board at Southern California Eye Institute. All participants provided written informed consent.

London Life Sciences Prospective Population (LOLIPOP). Approval was obtained from the London-Fulham Research Ethics Committee (ref 07/H0712/150). All participants gave an written informed consent.

Mexican American Study of Coronary Artery Disease (MACAD). Approval was granted by Human Subjects Protection Institutional Review Boards at the University of California at Los Angeles, University of Southern California, Lundquist/LABioMed/Harbor-UCLA and Cedars-Sinai Medical Center.Mexico City (MC). Approval was obtained from Institutional Review Boards at the Ethics and Scientific Commission members and the AUTHORIZATION is issued with registration number R-2011-785-018 and the Conacyt SALUD-2010-02-150352. In Canada, approval was obtained from the Research Ethics Board from the University of Toronto (Protocol 15770).

Multi-Ethnic Study of Atherosclerosis (MESA). Approval was obtained from Institutional Review Boards at the University of Washington, Wake Forest School of Medicine, Northwestern University, University of Minnesota, Columbia University, Johns Hopkins University, Cedars-Sinai Medical Center, and the University of California at Los Angeles.

Metabolic Syndrome in Men (METSIM). Approval was granted by the Ethics Committee of the University of Kuopio and the Kuopio University Hospital. All participants gave written informed consent.

Mass General Brigham Biobank (MGB). The MGB Biobank protocol and informed consent documents are reviewed annually by the Partners-MGB Institutional Review Board (#2009P002312). All patients who participate in the MGB Biobank are consented for their samples to be linked to their identified clinical information. They have also consented for their information to be used for a broad range of research and for their deidentified information to be shared outside of MGB.

Michigan Genomics Initiative (MGI). Approval was granted by the IRBMED Institutional Review Board of the University of Michigan. All participants gave written informed consent.

VA Million Veteran Program (MVP). All participating studies were conducted in compliance with the Declaration of Helsinki and comply with all relevant ethical and local regulatory requirements. Specifically, the contributing genetic association studies were approved by the Department of Veteran's Affairs central IRB.

Nagahama Study (NAGAHAMA). Approval was granted by the ethics committees of Kyoto University Graduate School of Medicine. Written informed consent was obtained from all participants.

Netherlands Epidemiology of Obesity (NEO). Approval was obtained from the Medical Ethics Committee of Leiden University Medical Center. All participants gave written informed consent.

Nurses Health Study (NHS). Approval was obtained from the Human Research Committee at the Brigham and Women's Hospital. All participants provided written informed consent.

NIDDM-Atherosclerosis Study Hispanic Cohorts (NIDDM). Approval was granted by Human Subjects Protection Institutional Review Boards at the University of California at Los Angeles, University of Southern California, City of Hope, Lundquist/LABioMed/Harbor-UCLA and Cedars-Sinai Medical Center.

Northwestern University Genetics (NUGENE). Approval was obtained from Institutional Review Boards at Northwestern University and Vanderbilt University

Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Approval was granted by the Ethics Committee of Uppsala University. All participants provided written informed consent.

Pakistan Risk of Myocardial Infarction Study (PROMIS). The study was approved by the Institutional Review Board of the Center for Non-Communicable Diseases Pakistan and by regional Ethical Review Committees in the different centres across Pakistan involved in the study. Institutional Review Boards at the National Institute of Cardiovascular Disorders, Karachi, Punjab Institute of Cardiology, Lahore, and Tabba Heart Institute, Karachi approved the study. All participants provided written informed consent.

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Approval was obtained from the Institutional Ethics Review Boards of Cork University (Ireland), Glasgow University (UK) and Leiden University Medical Center (The Netherlands). All participants gave written informed consent.

Sea Islands Genetic Network Reasons for Geographic and Racial Differences in Stroke (REGARDS). The REGARDS study protocol was approved by the institutional review boards of each participating institution, and written informed consents were obtained from all participants.

Ragama Health Study (RHS). Approval was obtained from Institutional Review Boards at the National Center for Global Health and the University of Kelaniya (P38/09/2006). All participants provided written informed consent.
Rotterdam Study (RS). Approval was granted by the Institutional review Board at Erasmus University Medical Center. All participants provided written informed consent.

Shanghai Breast Cancer Study and Shanghai Women's Health Study (SBCS/SWHS). Approval was obtained from Institutional review Boards at Vanderbilt University Medical Center and Shanghai Cancer Institute. A written informed consent form was obtained from all study participants.

Singapore Chinese Eye Study (SCES). The study adhered to the Declaration of Helsinki. Ethical approval was obtained from the SingHealth Institutional Review Board and National University of Singapore Institutional Review Board. Written informed consent was obtained from all participants.

Starr County Health (SCH). All protocols were reviewed and approved by the Institutional Committee for the Protection of Human Subjects (HSC-SPH-02-042). All participants provided written informed consent permitting the collection and sharing of data.

Singapore Chinese Health Study (SCHS). Approval was obtained from the Institutional Review Board at the National University of Singapore. All participants provided written informed consent.

Slim Initiative for Genomic Medicine in the Americas (SIGMA). Approval was obtained from the Institutional Review Board of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. All participants provided written informed consent.

Singapore Malay Eye Study (SIMES). The study adhered to the Declaration of Helsinki. Ethical approval was obtained from the SingHealth Institutional Review Board and National University of Singapore Institutional Review Board. Written informed consent was obtained from all participants.

Singapore Indian Eye Study (SINDI). The study adhered to the Declaration of Helsinki. Ethical approval was obtained from the SingHealth Institutional Review Board and National University of Singapore Institutional Review Board. Written informed consent was obtained from all participants.

Samsung Medical Center (SMC). Approval was obtained from the Institutional Review Board of the Samsung Medical Center (No. 2004-12-005). All participants provided written informed consent.

Seoul National University Hospital (SNUH). The Institutional Review Board of the Biomedical Research Institute at Seoul National University Hospital approved the study protocol (1205–130–411). Written informed consent was obtained from each participant.

Taiwan Metabochip Consortium Zhonghua (TAICHI-G). Approval was granted by Institutional Review Boards at Stanford University School of Medicine, Hudson-Alpha Biotechnology Institute, Lundquist/LABioMed/Harbor-UCLA, Cedars-Sinai Medical Center, Taichung Veterans General Hospital, Taipei Veterans General Hospital, National Health Research Institute, Tri-Service General Hospital, and National Taiwan University Hospital.

Taiwan Type 2 Diabetes (TWT2D). Approval was obtained from Institutional Review Boards at China Medical University Hospital, Chia-Yi Christian Hospital, and National Taiwan University Hospital.

Danish T2D Case-Control Study (UCPH). The studies included in the Danish T2D Case-Control Study (UCPH) were conducted in accordance with the Declaration of Helsinki II and were approved by the local Ethical Committees of Copenhagen County, the Capital Region of Denmark, or the Region of Southern Denmark.

UK Biobank (UKBB). Approval was obtained from the North West Centre for Research Ethics Committee (11/NW/0382).

Uppsala Longitudinal Study of Adult Men (ULSAM). Approval was granted by the Ethics Committee of Uppsala University. All participants provided written informed consent.

Wake Forest School of Medicine (WFSM). Approval was granted by the Institutional Review Board at Wake Forest School of Medicine. All participants provided written informed consent.

Women's Health Initiative (WHI). Approval was granted by the Institutional review Board at the Fred Hutchinson Cancer Research Centre in accordance with the US Department of Health and Human Services regulations at 45 CFR 46 (approval number IR# 3467-EXT). All participants provided written informed consent. Additional written consent to review medical records was obtained. The Fred Hutchinson Cancer Research Centre has an approved FWA on file with the Office for Human Research Protections under assurance number 0001920.

Wellcome Trust Case Control Consortium (WTCCC). Approval for the study was obtained from Peterborough & Fenland Local Research Ethics Committee, National Research Ethics Service, Leeds (East) Research Ethics Committee, South West Multicentre Research Ethics Committee, Tayside Committee on Medical Research Ethics and Oxford Tropical Research Ethics Committee.

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