Novel Methods for Multi-ancestry Polygenic Prediction and their Evaluations in 5.1 Million Individuals of Diverse Ancestry

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Abstract

Polygenic risk scores are becoming increasingly predictive of complex traits, but their suboptimal performance in non-European ancestry populations raises questions about their clinical applications and impact on health inequities. We develop CT-SLEB, a powerful and scalable method to calculate PRS based on ancestry-specific GWAS summary statistics from multi-ancestry training samples by integrating multiple techniques, including clumping and thresholding, empirical Bayes and super learning. We evaluate the performance of the proposed method and nine alternatives using large-scale simulated GWAS on ~19 million common variants and large datasets from 23andMe Inc., the Global Lipids Genetics Consortium, All of Us and UK Biobank, which include up to 1.18 million individuals from four non-European populations across thirteen complex traits. Results show that the proposed method can substantially improve the performance of PRS in non-European populations relative to simple alternatives and has comparable or superior performance relative to a recent method that requires a higher order of computational time. Furthermore, our simulation studies provide novel insights to sample size requirements and the effect of SNP density on multi-ancestry risk prediction.

Introduction

Genome-wide association studies (GWAS) have identified tens of thousands of single nucleotide polymorphisms (SNPs) associated with complex traits and diseases[1,2]. Polygenetic risk scores (PRSs), which summarize the combined effect of individual SNPs, have the potential to improve risk stratification for various diseases and conditions[3–13]. However, GWAS to date have mostly been conducted in populations predominately comprised of European (EUR) origin individuals[14]. Consequently, the PRSs generated from these studies tend to underperform in non-EUR populations, particularly in African (AFR) ancestry populations[9,15–18]. The lack of representation of non-EUR populations in PRS research has thus raised concerns that the use of current PRSs for clinical applications may exacerbate health inequities[19–22].

In addition to the critical importance of addressing inequalities in representation of non-EUR population in genetic research, there is also an important need to develop statistical methods that leverage genetic data across populations to develop better performing PRS. Most of the PRS methods to date have been developed to analyze data from a single ancestry group[23–32], and subsequently, their performance was primarily evaluated for risk prediction in EUR populations[4–6,8–11]. While the same methods can also be used to build PRS in non-EUR populations, the resulting PRS, irrespective of the methods, tend to have limited performance due to limited sample sizes of the training datasets compared to sample sizes in EUR populations[15,20]. Some studies have conducted meta-analyses of GWAS across diverse populations to develop an underlying multi-ancestry PRS[33–35]. While such an approach may lead to a single PRS that performs more “equally” across diverse groups, it does not account for heterogeneity in linkage disequilibrium (LD) and effect sizes across populations and not designed for deriving the best PRS possible for each of the underlying populations[36,37].

Recent methods have focused on developing more optimal PRS in non-EUR populations by combining available GWAS from the target population of interest with “borrowed” information from larger GWAS in the EUR populations. One such study developed PRS in separate populations and then combined the PRS by optimally

weighting them to maximize performance in the target population[38]. Other studies have proposed Bayesian methods that leverage multivariate priors for effect-size distribution to borrow information across populations[36,39–41]. In spite of these developments, methods for building PRS leveraging multi-ancestry datasets remain limited. Both theoretical and empirical studies have indicated that the optimal method for building PRS depends on multiple factors[23,42,43], including sample size, heritability, effect-size distribution and LD, and thus exploration of alternative methods with complementary advantages are needed to build optimal PRS is any given setting. Moreover, and perhaps more importantly, evaluation of the scope of multi-ancestry methods for building improved PRS remains quite limited to date due to the lack of suitably large GWAS for various non-EUR populations, especially of African origin, where risk prediction remains the most challenging.

In this paper, we propose a computationally simple and powerful method for generating PRSs using GWAS across diverse ancestry population. The method, which we refer to as CT-SLEB, is a model-free approach and combines the strength of multiple techniques, including a two-dimensional extension of the popular clumping and thresholding (CT) method[23,24], a super-learning (SL) model for combining multiple PRS and an empirical-Bayes (EB) approach to effect-size estimation. We compare the performance of the proposed method with nine alternative methods based on large-scale simulated GWAS across five ancestry groups. In addition, we develop and validate population-specific PRS for thirteen complex traits using GWAS data from 23andMe, Inc., the Global Lipids Genetics Consortium (GLGC), All of Us (AoU) and UK Biobank (UKBB) across EUR ($N \approx 3.91$ million), AFR (primarily African American (AA), $N \approx 265$K), Latino ($N \approx 574$K), East Asian (EAS, $N \approx 270$K), and South Asian (SAS, $N \approx 77$K). Both simulation studies and empirical data analyses indicate that CT-SLEB is a scalable and powerful method for generating PRS for non-EUR populations. Further, our simulation studies and evaluation of various methods in large datasets provide insights into the future yield of multi-ancestry PRSs as GWAS in diverse populations continues to grow.

Results

Method overview

CT-SLEB is a method designed to generate multi-ancestry PRSs that incorporate existing large GWAS from EUR populations and smaller GWAS from non-EUR populations. The method has three key steps (**Figure 1, Supplementary Figure 1**): 1. Clumping and Thresholding (CT) for selecting SNPs to be included in a PRS for the target population; 2. Empirical-Bayes (EB) method for estimating the coefficients of the SNPs; 3. Super-learning (SL) model to combine a series of PRSs generated under different SNP selection thresholds. The method requires three independent datasets: (1) GWAS summary statistics from training datasets across EUR and non-EUR populations; (2) a tuning dataset for the target population to find optimal model parameters; and (3) a validation dataset for the target population to report the final prediction performance.

Two-dimensional Clumping and Thresholding

In step one, CT-SLEB uses two-dimensional clumping and thresholding on GWAS summary-statistics data to incorporate SNPs with either shared effects across the EUR and the target populations or population-specific effects in the target population (**Figure 1a**). Each SNP is assigned to the following two groups based on the p-value from the EUR and the target population: 1. SNPs with a p-value smaller in the EUR population; 2. SNPs with a p-value smaller in the target population or those which exist only in the target population. SNPs in the first group are ranked based on EUR p-value (smallest to largest) and then clumped using LD estimates from the EUR reference sample. SNPs in the second group are ranked based on the target population p-value and clumped using LD estimates from the target population reference samples. Then the clumped SNPs from the two groups are combined as a candidate set for the next step. In the thresholding step, p-value thresholds are varied over a two-dimensional set of grid points. Each dimension corresponds to the threshold used for the p-value obtained from one of the populations. At any given combination of thresholds, a SNP may be included in the target population PRS if the corresponding p-value from either the EUR or the target population achieves the corresponding threshold.

Empirical-Bayes Estimation of Effect Sizes

Since the effect sizes of SNPs are expected to be correlated across populations[44,45], we propose an EB method to efficiently estimate effect sizes for SNPs to be included in the PRSs (**Figure 1b**). Based on the selected SNP set from the CT step, we first estimate an underlying "prior" covariance matrix of effect sizes between the EUR population and the target population. Then, we estimate the effect size for each SNP in the target population based on the corresponding posterior mean, which weighs the effect-size estimate available from each population based on the bias-variance trade-off (**Methods**).

Super Learning

Previous research has shown that combining PRSs under different p-value thresholds can efficiently increase the prediction performance[26]. Thus, as a final step, we propose a super-learning model to predict the outcome using PRSs generated under different tuning parameters as training variables (**Figure 1c**). The super-learning model is a linear combination of different predictors based on multiple supervised learning algorithms[46–49]. The set of prediction algorithms can be self-designed or chosen from classical prediction algorithms. We use the R package SuperLearner version 2.0-26[50] and choose Lasso[51], ridge regression[52], and neural networks[53] as three different candidate models in the implementation. We train the super-learning model on the tuning dataset and evaluate the performance of the final PRS using the independent validation dataset.

*Design of Simulation Studies***.**

We conduct simulation studies to compare ten methods across five broad categories: 1. *single ancestry methods*, which utilize training and tuning data solely from the target population; 2. *EUR PR*S, generated using single ancestry methods to EUR only GWAS data; 3. *weighted PRS,* which applies a single ancestry PRS approach separately to the EUR and target population, and derives an optimal linear combination of the two; 4. *Bayesian method,* which assumes a multi-variate Bayesian framework and uses the

posterior mean of effect sizes to construct the PRS; and 5. our proposed approach CT-SLEB. The single ancestry methods include two representative PRS methods: CT[23,24] and LDpred2[25,32]. The EUR PRSs are generated based on CT and LDpred2. The weighted PRS approaches include three representative PRS methods: a weighted PRS based on CT, a weighted PRS based on LDpred2, and PolyPred-S+[54] that linearly combines PRSs using EUR and target population PRS from SBayesR[27], and EUR PRS from PolyFun-pred[55]. The PolyFun-pred approach integrates functional annotation information to identify causal variant across the genome and thus uses additional information that is not incorporated in the other methods compared. The Bayesian method include: 1. XPASS method[40], which assumes a multivariate normal distribution to model the effect-size and uses the posterior mean of the target population to construct PRS. 2. PRS-CSx[36], which uses a continuous shrinkage Bayesian framework to calculate the posterior mean of effect sizes for the EUR and the non-EUR populations, and subsequently derives an optimal linear combination of all populations using a tuning dataset. All methods are implemented using the target population and EUR population as training data to construct the PRS for the target population. Additionally, CT-SLEB and PRS-CSx are further evaluated using data from all five ancestries. For computational efficiency, most analyses are restricted to ~2.0 million SNPs included in Hapmap3 (HM3)[56], or the Multi-Ethnic Genotyping Arrays (MEGA)[57] chips array, or both. However, the PolyPred-S+ and PRS-CSx methods can currently only be implemented with ~1.3 million HM3 SNPs in the provided software, and thus the application of these methods in our analysis is also restricted to only the HM3 SNPs.

Simulation Study Results

Results from simulation studies **(Figure 2** and **Supplementary Figure 2-6)** show that generally multi-ancestry methods lead to the most accurately PRSs in different settings. When the training data sample size for the target population is small (**Figure 2a, Supplementary Figure 2a, 3-6 a**), PRSs derived from the single ancestry methods perform poorly compared to the EUR-based PRS. On the other hand, when the training sample size for the target population is large (**Figure 2b, Supplementary Figure 2b, 3-6 b-d**), PRSs generated by the single ancestry methods can outperform EUR PRS.

PRS generated from the multi-ancestry methods can lead to substantial improvement in either setting.

When only EUR and target population data are used to build the PRS, we observe that both CT-SLEB and PRS-CSx can lead to improvement over other candidate methods in most settings. When the sample size for target population is large, weighted LDpred2 has comparable performance as CT-SLEB and PRS-CSx. Between CT-SLEB and PRS-CSx, neither is uniformly superior to the other across all scenarios considered. When the sample size for the target population is relatively small (N = 15K), PRS-CSx often outperforms CT-SLEB when the degree of polygenicity is the highest ($p_{causal} = 0.01$) . On the other hand, in the same sample size setting, CT-SLEB often outperforms PRS-CSx by a notable margin when the degree of polygenicity is the lowest ($p_{causal} = 5 \times 10^{-4}$). When the sample size for the target population is larger (N=45K-100K), the difference between the two methods decreases**.** When all five ancestries data are used to build the PRS, CT-SLEB and PRS-CSx improves by 6.8% and 23.7% on average, respectively, compared to only using EUR and the target population data. PRS-CSx outperforms CT-SLEB in many settings (**Figure 2b**, **Supplementary Figure 2a-b, 3-6 b-d)**. Under different simulation settings, the number of SNPs used by CT-SLEB ranged from 549K to 933K, while PRS-CSx retained all HM3 SNPs (**Supplementary Table 1**).

In a comparison of runtime using data on chromosome 22 to construct PRS for AFR (**Methods, Supplementary Table 2**), we observed runtime of CT-SLEB is on average almost 25 times faster than that of PRS-CSx (4.35 vs. 109.11 mins) in two ancestries analyses, and 91 times faster than that of PRS-CSx in five ancestries setting (4.62 vs. 420.96 mins) using a single core with Intel E5-26840v4 CPU. Sensitivity analyses are conducted to evaluate the required tuning and validation sample size for CT-SLEB (**Supplementary Figure 7**). When the tuning and validation sample size is larger, the prediction performance on average will increase. Meanwhile, the performance of CT-SLEB is still robust when the tuning and validation sample size is around 2000. Additional sensitivity analyses are conducted to compare the performance of CT-SLEB and PRS-CSx when both methods are constrained to HM3 SNPs. Results show that

CT-SLEB maintains advantage over PRS-CSx in low polygenicity setting when training sample size is 15K or 45K (**Supplementary Figure 8a-b**). However, when training sample size is more than 80K, both methods have similar performance in low polygenicity setting (**Supplementary Figure 8c-d**).

Unequal predictive performance of PRS across different populations has been considered as a barrier to ethical implementation of the technology in healthcare. Thus, we examined how large the sample size one may need for training GWAS in various minority populations to bridge the gap in the performance of PRS in comparison to that of the EUR population. Results indicate that when effect sizes for shared causal SNPs are similar across populations (genetic correlation=0.8), the gap can be mostly eliminated for all populations except AFR when the sample size reaches between 45% to 80% of that of the EUR population (**Figure 3**, **Supplementary Figure 8**). For the AFR population, however, the sample size requirement can dramatically vary depending on the underlying genetic architecture of the traits. If the common SNP heritability is assumed to be the same for the AFR population as that of the other populations, then the sample size requirement for the AFR population is dauntingly large because of substantially smaller per-SNP heritability (**Figure 3a-b**, **Supplementary Figure 9a-b**). If we allow the per-SNP heritability to remain the same across populations, but heritability to vary proportionately to the number of common variants, then the sample size requirement for the AFR population is similar to those for the other minority populations (**Figure 3c-d**, **Supplementary Figure 9c)**.

A major advantage of CT-SLEB over PRS-CSx is its computational scalability of the former method to handle much larger number of SNPs. Thus we use CT-SLEB to investigate the effect of SNP density on PRS performance by considering three different SNP sets to be used for PRS building: (1) ~1.3 million SNPs represented in HM3[56] (2) ~2.0 million SNPs that include all HM3 SNPs and additional SNPs represented in the MEGA array (3) All ~19 million common SNPs included in the 1000 Genomes Project (Phase 3)[58] which were used to generate the traits in our simulation studies. We observe that in general performances of PRS in various US minority populations can be

substantially enhanced by inclusion of SNPs in denser panels, and the benefit due to denser panels is more enhanced when the sample size for the target population is larger and in settings where the proportions of causal SNPs are smaller (**Figure 4 and Supplementary Figure 10**).

23andMe data analysis results

We develop and validate population-specific PRS for seven complex traits using GWAS data from 23andMe, Inc. (**Methods, Supplementary Table 3-4**). We conduct GWAS using a training dataset for each population adjusting for principal component (PC) 1-5, sex and age following standard quality control (**Methods**). The Manhattan plots and QQ plots for GWAS are shown in **Supplementary Figures 11-17**, and no inflation is observed given the genomic inflation factor (**Supplementary Table 5**). We estimate heritability for the seven traits in the EUR population using LD-score regression[59] (**Supplementary Table 6, Methods**).

Results for heart metabolic disease burden and height (**Figure 5, Supplementary Table 7**) show a similar pattern as our simulation studies. The PRS-CSx using five ancestries generally lead to the best performing PRS across different populations. When only EUR and the target population data are used, both CT-SLEB and PRS-CSx led to good performance across different populations. Compared to the best performing EUR or single ancestry PRS, the relative gain is often large, especially for the AA population. The weighted method did not perform well for the AA population, but it substantially improved performance compared to each component PRS (EUR and single ancestry) for other populations. PolyPred-S+ has comparable performance as PRS-CSx and CT-SLEB on EAS and SAS population, but significantly worse on AA population. We also observe that even with the best performing method and large sample sizes across all populations, a significant gap remains for the performance of the PRSs in non-EUR populations compared to those in the EUR population (**Figure 5**).

We also observe similar trends for the analyses of 23andMe data for the five binary traits: any cardiovascular disease (any CVD), depression, migraine diagnosis, morning

person, and sing back musical note (SBMN) (**Figure 6, Supplementary Table 7**). For most settings, CT-SLEB, PRS-CSx and PolyPred-S+ often produce the best performing PRS and often lead to substantial improvement over best EUR PRS or single ancestry PRS. For CVD, which is the clinically most relevant trait for risk prediction and preventive intervention, we observe that CT-SLEB tends to outperform PRS-CSx and PolyPred-S+ by a notable margin except for the EAS population. We also observe that for the AFR population, which are particularly underrepresented in genetic research, CT-SLEB outperforms PRS-CSx and PolyPred-S+ by a notable margin for several traits (e.g., CVD and morning person). In contrast, PRS-CSx and PolyPred-S+ outperforms CT-SLEB by a significant margin for predicting migraine diagnosis and SBMN in the SAS population. Similar to the continuous traits, we also observe that even with best performing methods and substantially large GWAS in a number of non-EUR populations, major gap often remains for the performance of PRS in these populations compared to those for the EUR population.

GLGC and AoU data analysis results with UKBB as validation dataset

We develop and validate population-specific PRS using GWAS summary data for four traits from GLGC: high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), log triglycerides (logTG) and total cholesterol (TC), and two traits from AoU: height and body mass index (BMI) (**Methods, Supplementary Table 4, 8**). The method is evaluated using individual level data from UKBB (**Supplementary Table 9**). The Manhattan plots and QQ plots for GWAS are shown in **Supplementary Figures 18-23**, and no inflation is observed given the genomic inflation factor for most ancestries other than height for Latino population in AoU ($\lambda_{1000} = 1.04$, **Supplementary Table 5**). We estimate heritability for the four traits in the EUR population using LD-score regression[59] (**Supplementary Table 6, Methods**).

In the data analyses using the GLGC data, CT-SLEB, PRS-CSx and PolyPred-S+ outperform the other approaches (**Figure 7**). Among these three methods, CT-SLEB demonstrates superior performance in the AFR population. For example, CT-SLEB leads to an improvement of 140% and 66.4% in adjusted R^2 for log-TG and LDL,

respectively, compared to the PRS-CSx method. This highlights the advantage of model-free approach CT-SLEB in handling biomarker traits, which can be associated with some SNPs with unusually large effects. On the other hand, PRS-CSx clearly outperforms CT-SLEB on the EAS population. For instance, for log-TG and LDL, the ratio of the adjusted R^2 between CT-SLEB and PRS-CSx is only 89.8% and 52.9%, respectively. These results show importance of generating PRS using multiple alternative methods in multi-ancestry settings. Another interesting observation is that, for LDL and TC, the PRS generated by both CT-SLEB and the five ancestries PRS-CSx demonstrated superior performance in the AFR population when compared to the performance of the corresponding EUR-PRSs in the European population (**Figure 7**). Finally, in AoU data analyses, we observe CT-SLEB performs better in predicting BMI, while PRS-CSx has better performance in predicting height, but both show comparable performance to each other (**Figure 8**).

To have a direct comparison between CT-SLEB and PRS-CSx, we report the prediction performance R^2 (continuous traits) or logit-scale variance (converted from Area under the ROC curve (AUC) for binary traits, **Supplementary Note**) between CT-SLEB and PRS-CSx and then average over the thirteen traits within each ancestry in data analyses of 23andMe, GLGC and AoU (**Supplementary Table 10**). When only the EUR and the target population data are used for PRS construction, the averaged performance ratio between CT-SLEB and PRS-CSx is 144%, 88.5%, 103% and 92.1% for AFR (primarily AA), EAS, Latino, SAS, respectively. When data from five ancestries or three ancestries (AoU) is used for PRS construction, the averaged performance ratio is 143%, 91.7%, 94.5%, 89.6% for AFR (primarily AA), EAS, Latino, SAS, respectively.

Discussion

In summary, we have proposed CT-SLEB as a powerful and computationally scalable method to generate optimal PRS across ancestrally distinct groups by utilizing GWAS across diverse populations. We compare the performance of CT-SLEB with those from a variety of both simple and complex methods, in large-scale simulation studies and very large datasets. Results indicate that there is not a uniformly best performing

method across all scenarios, and it is important to generate PRS using alternative methods across multi-ancestries. Encouragingly, however, the CT-SLEB method led to marked improvement in performance of PRS compared to alternatives in AFR origin populations where polygenic prediction has been most challenging. Computationally, CT-SLEB is an order of magnitude faster than a recently proposed Bayesian method, PRS-CSx[36], and can more easily handle much larger SNP contents and additional populations.

A unique contribution of our study is the evaluation of a variety of PRS methodologies in the unprecedented large and diverse datasets from the 23andMe, Inc., GLGC, AoU and UKBB GWAS datasets. Our findings provide important insights into the future yield of emerging large multi-ancestry GWAS. Adult height is often used as a model trait to explore the genetic architecture of complex traits and the potential for polygenic prediction. We observe that the standard CT method, when trained in ~2 million EUR individuals from 23andMe data, leads to a PRS for the underlying population with a prediction R^2 of approximately 0.276. Application of LD-score regression to the same 23andMe data leads to an estimated GWAS heritability of height of 0.395, indicating that the PRS has achieved about 69.8% (0.276/0.395) of its maximum potential in the 23andMe EUR population. We observe, however, that even with the best method and large sample size of the 23andMe GWAS (N_{Latino}~350K and N_{AFR} ~100K), the highest prediction accuracy of height PRS for non-EUR populations among all the methods is substantially lower compared to that of the EUR population (Relative R^2~0.48 (0.133/0.276) for AFR, 0.76 (0.210/0.276) for EAS, ~ 0.86 (0.237/0.276) for Latino, and ~ 0.80 (0.222/0.276) for SAS compared to that of EUR. The average relative R^2 (continuous traits) or logit-scale variance (binary traits) for AFR, EAS, Latino, and SAS across the thirteen evaluated traits is 0.50, 0.76, 0.77, and 0.79, respectively (**Supplementary Table 11**).

We also observe similar patterns for other traits, including disease outcomes for which risk prediction is of most interest. For CVD, for example, the CT method, when trained in a sample of ~700K cases and ~1.3 million controls from the EUR population,

produces a PRS that by itself has a prediction accuracy of the AUC as 0.65. For other populations, in some of which the sample size is considerably large ($N_{case}/N_{control}$ =32K/66K for AA and $N_{case}/N_{control}$ =84K/270K for Latino populations) but still much smaller than that of the EUR population, the AUCs for best performing PRSs are close to 60% or lower. Further, the sample size is not the only driving factor for differential performances of PRS across populations. For example, the performance of the best performing CVD-PRS for the Latino and South Asian populations are very similar even though the sample size for the later population is much smaller. Collectively, these and additional results from simulation studies, indicate that bridging the gap between PRS performance across populations will require much more parity in the sample size of the underlying GWAS.

Both our simulation studies and data analyses indicate that no single PRS method is expected to be uniformly most powerful in all settings. In the analysis of GLGC data, for example, we found CT-SLEB led to improvement in PRS performance by a large margin compared to PRS-CSx for the AFR population, but the converse was true for the EAS population. In general, the optimal method for generating PRS will depend on the nature of the underlying multivariate effect-size distribution of the traits across different populations. While Bayesian methods, in principle, can generate the optimal PRS under correct specification of underlying effect-size distribution[25,32,36,40], modeling of effect-size distribution in multi-ancestry settings can be challenging. In the analysis of lipid traits in GLGC, for example, we found the Bayesian methods could not account well for existence of large-effect SNPs in the AFR population due to inadequacy of the underlying model for the effect-size distribution. The CT method and their extensions, on the other hand, while they do not require strong modeling assumptions about effect-size distribution, they do not optimally incorporate LD among SNPs. Our analysis reveals advantages of alternative methods in different settings by contrasting of results across a variety of complex traits which are known to have distinct architecture in terms of heritability, polygenicity and number of clusters of distinct effect-sizes[60,61]. We thus advocate that in future applications, researchers consider generating and evaluating a variety of PRS obtained from complementary methods. As different PRS may contain

some orthogonal information, at the end, instead of choosing one best PRS, the best strategy could be to combine them using a final super learning step.

Our study has several limitations. While sample sizes for 23andMe datasets are extremely large, the power of genetic risk prediction is likely to have been blunted in this population, compared to other settings, due to the presence of a higher level of environmental heterogeneity. For example, a recent study[62] reported achieving prediction R^2 for height of ~41% for the EUR individuals within the UKBB using a PRS developed on ~1.1 million individuals from the UKBB (N=400K) and 23andMe (N=700K). In comparison, the PRS prediction R^2 for height we could achieve within 23andMe EUR population is only ~30% despite doubling the sample size of the training dataset. We, however, also note that the estimate of heritability in 23andMe ($h^2_{SNP} = 0.395$) is substantially smaller than those previously reported[63,64] based on the UKBB ($h^2_{SNP} \sim 0.5 - 0.7$), which is potentially due to the LD differences between 23andMe and 1000 Genomes Project. When we compare the results across the two studies using prediction R^2 relative to the underlying heritability of the respective populations, we do see a significant gain in performance due to the increased sample size of the current study. Thus, we believe that while caution is needed to extrapolate 23andMe study results to other populations, the relative performance of PRSs we observe across different methods and different ancestry groups within this population is likely to be generalizable to other settings.

While we have conducted large-scale simulation across various scenarios, the simulated genotype data from HapGen2 may not fully reflect the levels of differentiation within and across ancestries due to limited haplotype data within 1000 Genomes Project. A major limitation of our proposed method, as well as a variety of other existing methods, is that they are primarily designed to generate PRS across ancestrally distinct populations. However, many populations, such as the AFR and Latino origin in the US, are highly admixed, and for these populations, the development or clinical reporting of PRS can be improved by explicitly taking into account individual-level estimates of admixture proportions[65]. Additionally, our method assumes that individual-level data is

available for model tuning and validation, but this is not a fundamental limitation as summary-statistics-based methods[66,67] could also be used in these steps. Moreover, while we observe a consistent increase of five ancestries CT-SLEB over two ancestries CT-SLEB in simulations, the results of real data analyses don't show the same consistent pattern (**Figure 5-7**)**.** This may be due to the underlying effect-size across different ancestries being much more complex than the simulations, as the simulations only assume that causal SNPs effect-size follow a multi-variate normal distribution.

In conclusion, we have proposed a novel and computationally scalable method for generating powerful PRS using data from GWAS studies in diverse populations. Further, our simulation studies and data analysis across multiple traits involving large 23andMe Inc., GLGC, AoU and UKBB studies provide unique insight into what is likely to emerge from future GWAS in diverse populations for years to come.

Author contribution

H.Z. and N.C. conceived the project. H.Z., J.Z., J.J., J.Z., W.L. and R.Z. carried out all data analyses with supervision from N.C.; J.Z., J.O.C., Y.J. run GWAS for training data from 23andMe Inc. with the supervision from B.L.K.; R.Z. run GWAS for training data from AoU with the supervision from N.C. and H.Z.; H.Z., T.C., and D.O. developed the software and online resources for data sharing; H.Z., J.Z., J.J., J.Z., W.L., R.Z. and N.C. drafted the manuscript, and X.L., M.G.C. and T.U.A. provided comments. All co-authors reviewed and approved the final version of the manuscript. The following members of the 23andMe Research Team contributed to this study: Stella Aslibekyan, Adam Auton, Elizabeth Babalola, Robert K. Bell, Jessica Bielenberg, Katarzyna Bryc, Emily Bullis, Daniella Coker, Gabriel Cuellar Partida, Devika Dhamija, Sayantan Das, Sarah L. Elson, Nicholas Eriksson, Teresa Filshtein, Alison Fitch, Kipper Fletez-Brant, Pierre Fontanillas, Will Freyman, Julie M. Granka, Karl Heilbron, Alejandro Hernandez, Barry Hicks, David A. Hinds, Ethan M. Jewett, Yunxuan Jiang, Katelyn Kukar, Alan Kwong, Keng-Han Lin, Bianca A. Llamas, Maya Lowe, Jey C. McCreight, Matthew H. McIntyre, Steven J. Micheletti, Meghan E. Moreno, Priyanka Nandakumar, Dominique T. Nguyen, Elizabeth S. Noblin, Jared O'Connell, Aaron A. Petrakovitz, G. David Poznik, Alexandra Reynoso, Morgan Schumacher, Anjali J. Shastri, Janie F. Shelton, Jingchunzi Shi, Suyash Shringarpure, Qiaojuan Jane Su, Susana A. Tat, Christophe Toukam Tchakouté, Vinh Tran, Joyce Y. Tung, Xin Wang, Wei Wang, Catherine H. Weldon, Peter Wilton, Corinna D. Wong.

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Code and Data availability

CT-SLEB package and tutorial: https://github.com/andrewhaoyu/CTSLEB

P + T: https://www.cog-genomics.org/plink/1.9/

SCT and LDpred2: https://github.com/privefl/bigsnpr.

XPASS: https://github.com/YangLabHKUST/XPASS

PolyPred-S+: https://github.com/omerwe/polyfun

PRS-CSx: https://github.com/getian107/PRScsx

LDSC: https://github.com/bulik/ldsc

PLINK: https://www.cog-genomics.org/plink/1.9/

Simulated genotype data for 600K subjects from five ancestries: https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/COXHAP

GWAS summary level statistics for five ancestries from GLGC: http://csg.sph.umich.edu/willer/public/glgc-lipids2021/results/ancestry_specific/

The full GWAS summary statistics for the 23andMe discovery data set could be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit

https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data. Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services.

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Online Methods

We assume there are $l = 1, \ldots L$ populations with $l = 1$ indexing the EUR population. We assume that for each population, summary-statistics data from underlying GWAS are available in the form of $(\hat{\beta}_{kl}, s_{kl}, p_{kl})$ for $k = 1,2, \ldots, K_L$ SNPs, where $\hat{\beta}, s$ and p denote estimates of effect-size, standard errors and p-values associated with individual SNPs, respectively. We further assume that additional datasets are available for each target population of interest, which could be split into tuning and validation sets. Our proposed CT-SLEB method contains three steps: 1. Two-dimensional clumping and thresholding (CT); 2. EB procedure; 3. Super-learning algorithm, which will be described in detail in the following three subsections.

CT. In this step, we extend the traditional CT to a two-dimensional setting so that PRS for a target population can be built using approximately independent SNPs that show significant association in at least one of the two populations (majority population and the target population). The CT method has two components, the Clumping step and the Thresholding step. In the two-dimensional setting where the lead SNPs might be informed by GWAS of either the EUR or target population, it is unclear what reference sample is the most suited for LD clumping. After initial exploration of alternative approaches through simulation studies, we find the most informative approach is to split the SNPs into two sets depending on which population they show stronger signals and then perform LD clumping for each set separately based on the reference sample for the respective population. For the thresholding step, we select SNPs based on two distinct thresholds for their respective p-values in the two populations. As the optimal threshold for p-value selection is known to depend on sample size for underlying GWAS[24,42,43], and sample sizes for GWAS across EUR and minority populations are highly differential, we anticipate (and confirm through simulation studies) that a two-dimensional approach for threshold selection is more optimal than using a single p-value threshold across both populations. Following, we describe details of the CT step:

1. The clumping r^2-cutoff and base size of the clumping window size w_b vary across (0.01, 0.05, 0.1, 0.2, 0.5, 0.8) and (50kb, 100kb), respectively. The

clumping window size w_s is defined as w_b/r^2 because LD is inversely proportional to the genetic distance between variants[26,68].

2. Select all SNPs with smaller p-values in EUR ($p_{k1} < p_{k2}$), and then, clump based on p_{k1} using LD estimates from the EUR reference samples with selected r^2 and w_s.
3. Select all variants with smaller p-values in the target population ($p_{k2} < p_{k1}$) and the population-specific SNPs, and then, clump based on p_{k2} using LD estimates from the reference samples of the target population with the same r^2-cutoff and w_b.
4. Combine the post-clumping variants from the second and third steps as the candidate variants set.
5. Define two different p-value cutoffs (p_{t1}, p_{t2}) for the EUR and the target population. A variant is selected if $p_{k1} < p_{t1}$ or $p_{k2} < p_{t2}$. We allow p_{t1} and p_{t2} to vary in the set: $(5 \times 10^{-8}, 5 \times 10^{-7}, 5 \times 10^{-6}, \dots, 5 \times 10^{-1}, 1.0)$. With the cross combination of p_{t1} and p_{t2}, a total of 81 different p-value cutoffs are applied.
6. With the cross combination of p_{t1}, p_{t2}, r^2 and w_b, a total of 972 PRSs (6 r^2 thresholds * 2 w_b windows * 81 value thresholds) are evaluated on the tuning dataset using estimated regression coefficients ($\hat{\beta}_{k2}$) from GWAS of the target population.

EB to calibrate regression coefficients. In the CT step above, we use $\hat{\beta}_{k2}$ from the target population to calculate PRS. However, $\hat{\beta}_{k2}$ can be noisy when the GWAS sample size of the target population is small. Meanwhile, given the high genetic correlation across different ancestries[44,45], effect sizes from other populations can be used to calibrate the regression coefficients for the PRS. Although we only use p-values from GWAS for the EUR and the target population for selecting SNPs in the CT step, the EB step takes advantage of existing GWAS from multiple populations. Suppose $\hat{\boldsymbol{u}}_k = (\hat{u}_{k1}, \dots, \hat{u}_{kL}) = (\hat{\beta}_{k1}\sqrt{2f_{k1}(1-f_{k1})}, \dots, \hat{\beta}_{kL}\sqrt{2f_{kl}(1-f_{kL})})$, is the vector of the standardized effect-size for the kth SNP in L different populations, with $\hat{\boldsymbol{s}}_{\boldsymbol{k}}^* =$

$(s_{k1}^*, \dots, s_{kL}^*) = \left(s_{k1}\sqrt{2f_{k1}(1-f_{k1})}, \dots, \hat{s}_{kL}\sqrt{2f_{kL}(1-f_{kL})}\right)$ being the vector of the corresponding standard errors of $\widehat{\boldsymbol{u}}_k$. We assume that $\widehat{\boldsymbol{u}}_k | u_k \sim N(\boldsymbol{u}_k, \boldsymbol{\Sigma}_\mathbf{k})$, where $\boldsymbol{\Sigma}_\mathbf{k} = diag\{(\widehat{\boldsymbol{s}}_{\boldsymbol{k}}^*)^\mathbf{2}\}$ given that the GWAS for different populations are independent. Additionally, we assume that the prior distribution of the mean of $\widehat{\boldsymbol{u}}_k$ is $\boldsymbol{u}_k \sim N(\mathbf{0}, \boldsymbol{\Sigma}_\mathbf{0})$, which assumes the effect-size follows the strong negative selection model. By integrating the conditional and prior distribution, we can obtain the marginal distribution of $\widehat{\boldsymbol{u}}_k$ as $N(\mathbf{0}, \boldsymbol{\Sigma}_\mathbf{0} + \boldsymbol{\Sigma}_\mathbf{k})$. Suppose the SNP set selected from the CT step has K^* variants overlapped across all the populations. We estimate the prior covariance matrix $\boldsymbol{\Sigma}_\mathbf{0}$ using the K^*overlapped variants shared across all populations as:

$$\widehat{\boldsymbol{\Sigma}}_\mathbf{0} = \frac{1}{K^* - 1}\sum_{k=1}^{K^*} \widehat{\boldsymbol{u}}_k^T \widehat{\boldsymbol{u}}_k - \boldsymbol{\Sigma}_\mathbf{k}.$$

We note that we ignore any potential correlation across selected SNPs in this step, but the estimate is still expected to be consistent for $\boldsymbol{\Sigma}_\mathbf{0}$ which represents marginal variance-covariance matrices for effect sizes associated with an individual SNP across populations. Applying the Bayes formula, the posterior distribution of $\boldsymbol{u}_k$ becomes

$$\boldsymbol{u}_k | \widehat{\boldsymbol{u}}_k \sim N\left(\widehat{\boldsymbol{\Sigma}}_\mathbf{0}(\widehat{\boldsymbol{\Sigma}}_\mathbf{0} + \boldsymbol{\Sigma}_\mathbf{k})^{-\mathbf{1}} \widehat{\boldsymbol{u}}_k, \widehat{\boldsymbol{\Sigma}}_\mathbf{0}(\widehat{\boldsymbol{\Sigma}}_\mathbf{0} + \boldsymbol{\Sigma}_\mathbf{k})^{-\mathbf{1}} \boldsymbol{\Sigma}_\mathbf{k}\right).$$

The EB coefficients for the kth SNP are defined as:

$$\widehat{\boldsymbol{\beta}}_k^{EB} = \mathbf{F_k}\, \widehat{\boldsymbol{\Sigma}}_\mathbf{0}\left(\widehat{\boldsymbol{\Sigma}}_\mathbf{0} + \boldsymbol{\Sigma}_\mathbf{k}\right)^{-\mathbf{1}} \widehat{\boldsymbol{u}}_k,$$

where $\widehat{\boldsymbol{\beta}}_k^{EB}$ is a $L \times 1$ vector for the posterior effect-size of the kth SNP for in each of the L populations, and $\mathbf{F_k} = \mathrm{diag}\left\{\frac{1}{\sqrt{2f_{kl}(1-f_{kl})}}\right\}_{\mathrm{L}\times\mathrm{L}}$ is the scaling matrix to scale effect sizes from the standardized scale back to the original scale. Preliminary simulation studies indicate that EB step of effect-size calibration leads to distinct improvement in PRS performance (compared to using effect-size estimates from the target population) irrespective of all other steps.

To save computational time, we estimate $\widehat{\boldsymbol{\Sigma}}_0$ in the above step only once based on the SNP set that gives the best PRS in the CT step across all different p-value thresholds, r^2-cutoff, and window sizes. We then apply the same $\widehat{\boldsymbol{\Sigma}}_0$ to derive the EB-calibrated effect sizes for SNPs included in all different PRSs corresponding to cross combination

of p_{t1}, p_{t2}, r^2-cutoff and w_b. Using the EB-calibrated effect sizes, we can compute 972 PRSs for each population (6 r^2 thresholds * 2 w_b windows * 81 value thresholds). In all analyses, we compute the 1944 PRSs using EB-calibrated effect sizes of the target population and EUR. When more than two ancestries are involved, we use data from all populations to derive the EB estimates of effect-sizes for SNPs for each population (**Supplementary Note**). However, to save computational time at the super-learning step, we derive the final PRS for the target population by only incorporating the 1944 PRSs derived for the larger EUR population and the target population. All 1944 PRSs are used as input for the super-learning step to predict the outcome for the target population. Because many PRSs are highly correlated with each other, we filter out the highly redundant one with pairwise correlations higher than 0.98. In the simulations, 369 of the 1994 PRSs are kept on average after the filtering.

Super learning. We combine all PRSs generated from the above steps into an input dataset and train them on the tuning dataset to predict the outcome Y. The super-learning algorithm generates an optimally weighted combination from a set of distinct prediction algorithms[46–49] (**Supplementary Note**). The set of prediction algorithms can be self-designed or chosen from classical prediction algorithms e.g., Lasso[51], ridge regression[52], neural networks[53], etc. We use three different prediction algorithms implemented in the SuperLearner package[50] to generate the super learning estimate: Lasso[51], ridge regression[52] and neural networks[53]. For binary traits, since the ridge regression algorithm is currently not supported by the SuperLearner package now, we only use Lasso and neural network in the data analysis. To use AUC as the objective function, we use the flag “method = method.AUC” in the SupearLearner package.

Simulation. Large-scale multi-ancestry genotype data are generated using HAPGEN2 (version 2.1.2)[69] mimicking the LD of EUR, AFR, Americas (AMR), East Asia (EAS) and South Asia (SAS). The 1000 Genomes Project (Phase 3)[58] is used as the reference panel which include 503 EUR, 661 AFR, 347 AMR, 504 EAS and 489 SAS subjects. Biallelic SNPs with MAF more than 0.01 in any of the populations are kept in the reference panel, resulting in ~8.6 million SNPs for EUR, ~14.8 million SNPs for AFR,

~9.8 million SNPs for AMR, ~7.6 million SNPs for EAS, and ~9.0 million SNPs for SAS. The genotype data are generated with a total of ~19.2 million SNPs. The set of simulated variants for all five ancestries is same. Because allele frequencies vary across populations, a common SNP can be population-specific if its MAF is greater than 0.01 in only one population. The proportion of population-specific SNPs range from 2.92% for AMR to 43.84% for AFR, respectively (**Supplementary Figure 24**). If a particular variant's MAF is less than 0.01 in a given population, we don't include them in the PRS calculation for that population because the LD estimation for rare variants can be unstable. We simulate a total of 120,000 independent subjects for each of the population.

For generating trait values, we select causal SNPs randomly across the whole genome with the causal SNP proportion being set to 0.01, 0.001, or 5×10^{-4}. We consider two alternative models for generating heritability distribution within each population: (A) Constant common-SNP heritability. (B) Constant per-SNP heritability that implies the total heritability is proportional to the number of common SNPs. We also consider three different models for negative selection pattern: strong, mild and no negative selection.

We denote by u_{kl} the standardized effect-size for kth causal SNP for the lth population. Under strong negative selection and constant heritability model, the standardized effect-sizes are drawn from a multivariate normal distribution of the form:

$$u_{kl} \sim N\left(0, \frac{h^2}{C_l}\right), cov\left(u_{kl_1}, u_{kl_2}\right) = \frac{\rho h^2}{\sqrt{C_{l_1} C_{l_2}}},$$

where C_l is the number of causal SNPs with MAF > 0.01 in the lth population, the heritability h^2 associated with common SNPs for each population is set to 0.4, and the genetic correlation ρ is set to 0.8. We then generate the phenotype using linear model of the form $Y_{il} = \sum_{k=1}^{C_l} \frac{G_{ikl}}{\sqrt{2(f_{kl}(1-f_{kl})}} u_{kl} + \epsilon_{il}$ for the ith subject in the lth population, where $f_{kl}$is the effect allele frequency for the kth causal SNP in lth population. The error terms are generated as $\epsilon_{il} \sim N(0,1-h^2)$. We also consider mild negative selection ($u_{kl}^2 \propto [f_{kl}(1-f_{kl})]^{0.75}$) and no negative selection ($u_{kl}^2 \propto [f_{kl}(1-f_{kl})]$) scenarios (see

Supplemental Notes for details). Finally, we simulate data under an assumption of total heritability of all ~19 million SNPs being 0.4 across all populations, but the common SNP heritability varying proportionately to their number within each the populations. The model assumes per SNP heritability to be the same across all populations and thus leads to the common SNP heritability value of 0.32, 0.21, 0.16, 0.19 and 0.17 for AFR, AMR, EAS, EUR and SAS, respectively. The genetic correlation is set to 0.8 or 0.6.

We set the training sample sizes for each target population to 15,000, 45,000, 80,000, or 100,000. We generate GWAS summary statistics for each population based on the training samples using PLINK version 1.90 with the command "--linear". We fixed the sample sizes for the EUR population at 100,000. We further simulate the tuning and validation dataset of size 10,000 for each target population. The final prediction R^2 is reported as the average of ten independent simulation replicates for each simulation setting. For evaluating CT-SLEB that incorporates data across all five ancestries, we assume the training sample size for the each of the other non-EUR populations to be the same as that of the target population.

Existing PRS methods. The CT method selects clumped SNPs with different p-value thresholds and picks a single optimal PRS based on its performance on the tuning dataset. We implement CT using PLINK version 1.90[70] with the clumping step command "--clump --clump-r2 0.1 --clump-kb 500". We estimate LD based on 3,000 randomly selected unrelated subjects from the training dataset for each population. We set the candidate p-value thresholds to be $(5 \times 10^{-8}, 1 \times 10^{-7}, 5 \times 10^{-7}, 1 \times 10^{-6}, \ldots, 5 \times 10^{-1}, 1.0)$ and for computing PRS, we use the PLINK command "--score no-sum no-mean-imputation". The optimal p-value threshold is determined based prediction R^2 (variation explained by the corresponding PRS) on the tuning dataset.

The LDpred2 method infers SNP effect sizes by a shrinkage estimator that combines GWAS summary statistics with a prior on effect sizes while leveraging LD information from an external reference panel. LDpred2 is implemented using the R package "bigsnpr"[32]. The tuning parameters included are: (1) the proportion of causal SNPs, with

candidate values set to a sequence of length 17 that are evenly spaced on a logarithmic scale from 10^{-4} to 1; (2) per-SNP heritability, with candidate values set to 0.7, 1, or 1.4 times the total heritability estimated by LD score regression divided by the number of causal SNPs; (3) “sparse” option, which is set to “yes” or “no” (the “sparse” option sets some weak effects to zero). The method selects tuning parameters based on the performance on the tuning dataset.

The EUR PRS based on CT or LDpred2 are built based on training dataset from the EUR population and estimates tuning parameters based on tuning sample for the EUR population. When the EUR PRSs are evaluated in the target population, we exclude the SNPs that do not exist in the target population.

The weighted-PRS linearly combines the CT or LDpred2 PRS generated from the EUR and from the target population. The weights for EUR PRS and for the target population PRS in the linear combination are estimated using the tuning dataset from the target population through a linear regression. We implement the weighted-PRS using R version 4.0.0.

The PolyPred-S+ method consists of a PolyFun-pred predictor trained on the EUR population and two SBayesR predictors that use the training data from the EUR and the target population respectively. On a tuning dataset from the target population, PolyPred-S+ performs the non-negative least squares regression to compute the mixture weights and linearly combines the predictors. In PolyFun-pred, PolyFun leverages genome-wise functional annotations to compute the prior causal probabilities, which are fed into the fine-mapping method SuSiE for the posterior causal effect estimation. On the other hand, SBayesR estimates the posterior tagging effects by posing a finite normal mixture prior on the effect sizes. For PolyFun-pred, we use the precomputed prior causal probabilities provided by the authors, extract the LD information using EUR population in 1000 Genomes Project (Phase 3), and assume 10 causal SNPs per locus. Using GCTB (2.03 beta version), we train SBayesR with the sparse shrunk LD matrix for HapMap3 variants published by the SBayesR authors. Currently, the shrunk LD matrix

are only available for EUR populations. Therefore, SBayesR predictors for EUR and the target population both used the shrunk LD matrix for EUR. We specify the model parameters and the MCMC settings in the same way as the PolyPred-S+ authors did in their UKBB simulations.

The XPASS method leverages the genetic correlation between the target and the EUR population by assuming a bivariate normal distribution with non-zero covariance for the pairs of effect sizes that correspond to the same SNP in two populations. It can incorporate population-specific covariates as fixed effects to enhance the accuracy of their weight estimation. For each population, we extract the top 20 PCs from the reference genome as the covariates. When estimating the LD matrices, ancestry-specific reference data is inputted in the function. LD matrices are estimated based on the LD blocks for EUR to all datasets, given that XPASS package only offers choices of EUR and EAS.

The PRS-CSx method estimates population-specific SNP effect sizes based on a Bayesian framework using continuous shrinkage priors to jointly model the GWAS summary statistics from multiple populations. Besides the Bayesian modeling step, PRS-CSx further conducts a step similar to weighted-PRS, which is to linearly combine the PRS based on the posterior effect-sizes obtained from the EUR and the target population with the weights in the linear combination being estimated based on the tuning dataset of the target population. We implemented PRS-CSx following the guidance provided in https://github.com/getian107/PRScsx. We set the hyperparameters a and b in the gamma-gamma prior to their default values of 1 and 0.5, respectively. Further, the parameter ϕ is varied over the default set of values 10^{-6}, 10^{-4}, 10^{-2}, and 1. The optimal ϕ is determined based on the performance on the tuning dataset.

Runtimes and memory usage. The computation time and memory usage of CT-SLEB (two ancestries), CT-SLEB (five ancestries), and PRS-CSx are compared based on

their performance on chromosome 22 and assuming AFR is the target population. All analyses are performed using a single core with Intel E5-26840v4 CPU. The reported performance is averaged over 100 replicates. The training dataset includes GWAS summary statistics for AFR (N_{GWAS}=15,000) and for EUR (N_{GWAS}=100,000) population. The tuning dataset and validation dataset each contains 10,000 subjects. For five ancestries analyses, the training GWAS sample sizes for AMR, EAS and SAS are all set to 15,000.

23andMe Data analysis. The individuals included in our analyses are part of the 23andMe participant cohort. All these individuals included have provided informed consent and answered surveys online according to our human subject protocol reviewed and approved by Ethical & Independent Review Services, a private institutional review board (http://www.eandireview.com). Detailed information about genotyping, quality control, imputation, removing related individuals, and ancestry determination is provided in **Supplementary Note**. Participants were included in the analysis based on consent status as checked when data analyses were initiated.

The analyses include five ancestries: AA, EAS, EUR, Latino, and SAS. Meanwhile, the analyses include two continuous and five binary traits: 1. Heart metabolic disease burden 2. Height 3. Any CVD 4. Depression 5. Migraine Diagnosis 6. Morning Person 7. SBMN. We randomly split the data for each population into training, tuning, and validation datasets with the proportion of 70%, 20%, and 10%, with detailed sample size in **Supplementary Table 3**. We perform GWAS for the seven traits using the training dataset for each population, adjusting for PC 1-5, sex, and age using standard quality control procedures (**Supplementary Note**). SNPs with MAF > 0.01 in at least one of the five populations are kept in the analyses. We further restrict analyses to SNPs that are on HM3 + MEGA chips with ~2.0 million SNPs. We use LDSC version 1.01[59] to estimate the heritability using the GWAS summary statistics of EUR populations for the seven traits. We estimate the LD score using the 503 unrelated samples of EUR ancestry from 1000 Genomes Project. We restrict heritability analyses to EUR populations since some

non-EUR populations don't have sufficient sample size to get stable estimate from LD-score regression.

We apply seven methods to compare PRS prediction performance, CT, LDPred2, best EUR PRS based on CT and LDpred2, weighted-PRS, PRS-CSx, CT-SLEB using data from EUR and the target population, and CT-SLEB using all five populations. Since individual-level data is not available in the training step, we use the reference data from the 1000 Genomes Project (Phase 3) to estimate the LD for each population. Specifically, we use AFR and AMR from the 1000 Genomes Project as the reference for the AA and Latino population in 23andMe, respectively. All PRS prediction performances are reported based on the independent validation dataset that is independent of the training and tuning datasets. To calculate the adjusted R^2 for continuous traits, we first regress the traits on covariates and then evaluate performance of the PRS to predict residualized trait values. To calculate the adjusted AUC for binary traits, we used the roc.binary function in the R package RISCA version 1.01[71].

GLGC Data analysis. The GWAS summary statistics of four blood lipids traits are obtained from the public available database of GLGC (http://csg.sph.umich.edu/willer/public/glgc-lipids2021/results/ancestry_specific/). UKBB data are removed from the GWAS summary statistics. The details of study design of study, genotyping, quality control and GWAS are described elsewhere[72]. The training data are available for four blood lipid traits: LDL, HDL, logTG, TC from five different ancestries: EUR, AFR (primarily AA), Latino, EAS, and SAS (**Supplementary Table 8**). The tuning + validation data from UKBB dataset are from EUR, AFR, EAS and SAS ancestries (**Supplementary Table 9**). Details of ancestry prediction of UKBB are described in **Supplementary Note**. Latino ancestries in UKBB can't not be well classified using the ancestry prediction algorithm, and the corresponding sample size is too low to provide meaningful comparison of methods. Therefore, Latino population is evaluated using UKBB data. The implementation of the ten different PRSs approaches follow the same steps as the 23andMe data analyses. We use the reference data from

the 1000 Genomes Project (Phase 3) to estimate the LD for each population. The adjusted R^2 are adjusted by sex, age and genetic PC1-10.

AoU Data analysis. The individuals included in our analyses are part of the AoU participant cohort. All these individuals' information have been collected according to AoU Research Program Operational Protocol (https://allofus.nih.gov/sites/default/files/aou_operational_protocol_v1.7_mar_2018.pdf). Detailed information about genotyping, ancestry determination, quality control, removing related individuals are listed in AoU Research Program Genomic Research Data Quality Report (https://www.researchallofus.org/wp-content/themes/research-hub-wordpress-theme/media/2022/06/All%20Of%20Us%20Q2%202022%20Release%20Genomic%20Quality%20Report.pdf).

The analyses include three ancestries: EUR, AFR, and Latino/Admixed American, and two continuous traits: 1. Height, 2. BMI. We perform GWAS for the two traits using the unrelated samples for each population, adjusting for PC 1-16, sex, and age, where some quality control steps are provided in AoU platform.

In AoU platform, the Whole Genome Sequencing (WGS) data and Array data are both provided, while the WGS data has fewer samples than Array data (98,590 WGS and 165,127 array samples, June 22, 2022, version). The quality control information and relatedness of samples are only provided within WGS data. For GWAS with respect to each population, we perform sample level quality control within WGS data. Due to computation burden, the analyses are conducted using the array SNPs with subjects that pass the quality control in the WGS data. SNPs with MAF > 0.01 in at least one of the three populations are kept, while we also restrict analyses to SNPs that are available on HM3 + MEGA chips. Since the analyses are constrained to Array data, all analyses are conducted using up to 800K SNPs (**Supplementary Table 4**). We use the reference data from the 1000 Genomes Project (Phase 3) to estimate the LD for each population.

The tuning + validation data from UKBB dataset are from EUR and AFR. Latino population is not evaluated on UKBB for the same reason as GLGC analyses. The implementation of the ten different PRSs approaches follow the same steps as the 23andMe data analyses. The adjusted R^2 are adjusted by sex, age and PC1-10.

Figure 1: CT-SLEB Workflow. The method contains three key steps: 1. Two-dimensional clumping and thresholding method for selecting SNPs (**Figure 1a**); 2. Empirical-Bayes procedure for incorporating correlation in effect sizes of genetic variants across populations (**Figure 1b**); 3. Super-learning model for combing the PRSs derived from the first two steps under different tuning parameters (**Figure 1c**). The GWAS summary-statistics data are obtained from the training data. The tuning dataset is used to train the super-learning model. The final prediction performance is evaluated using an independent validation dataset.

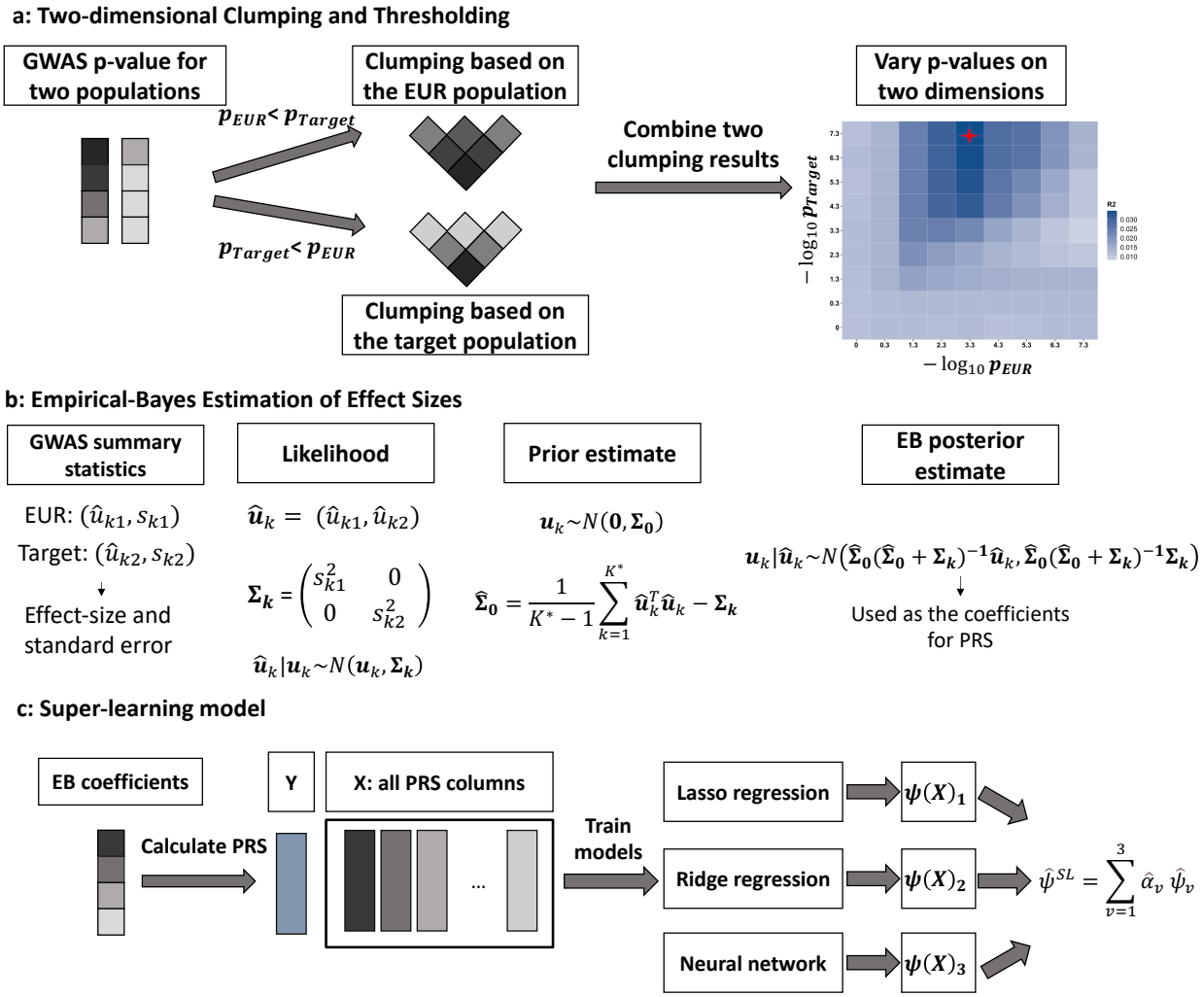
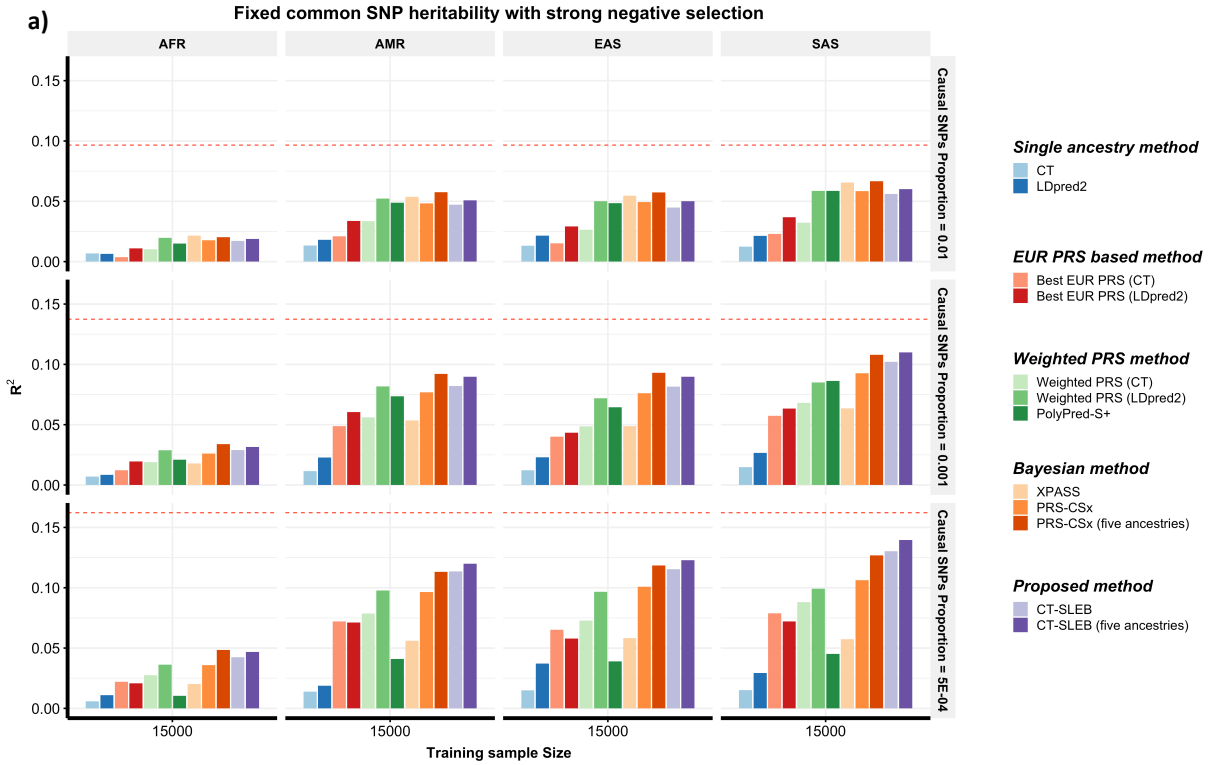


Figure 2: Simulation results of various PRSs methods in multi-ancestry settings. Each of the four non-EUR populations has a training sample size of **15,000 (Figure 2a) or 80,000 (Figure 2b)**. For the EUR population, the size of the training sample is set at 100,000. The tuning dataset includes 10,000 samples per population. Prediction R^2 values are reported based on an independent validation dataset with 10,000 subjects per population. Common SNP heritability is assumed to be 0.4 across all populations, and effect-size correlation is assumed to be 0.8 across all pairs of populations. The proportion of causal SNPs varies across 0.01 (top panel), 0.001 (medium panel), 5×10^{-4} (bottom panel), and effect sizes for causal variants are assumed to be related to allele frequency under **<u>a strong negative selection model</u>**. Data are generated based on ~19 million common SNPs across the five populations, but analyses are restricted to ~2.0 million SNPs that are used on Hapmap3 + Multi-Ethnic Genotyping Arrays chip. PolyPred-S+ and PRS-CSx analyses are further restricted to ~1.3 million HM3 SNPs. All approaches are trained using data from the EUR and the target population. CT-SLEB and PRS-CSx are also evaluated using five ancestries data as training data. The red dashed line shows the prediction performance of EUR PRS generated using the single ancestry method (best of CT or LDpred2) in the EUR population.


a)
Fixed common SNP heritability with strong negative selection
AFR
AMR
EAS
SAS
Causal SNPs Proportion = 0.01
Causal SNPs Proportion = 0.001
Causal SNPs Proportion = 5E-04
R2
0.15
0.10
0.05
0.00
15000
Training sample Size
Single ancestry method
CT
LDpred2
EUR PRS based method
Best EUR PRS (CT)
Best EUR PRS (LDpred2)
Weighted PRS method
Weighted PRS (CT)
Weighted PRS (LDpred2)
PolyPred-S+
Bayesian method
XPASS
PRS-CSx
PRS-CSx (five ancestries)
Proposed method
CT-SLEB
CT-SLEB (five ancestries)

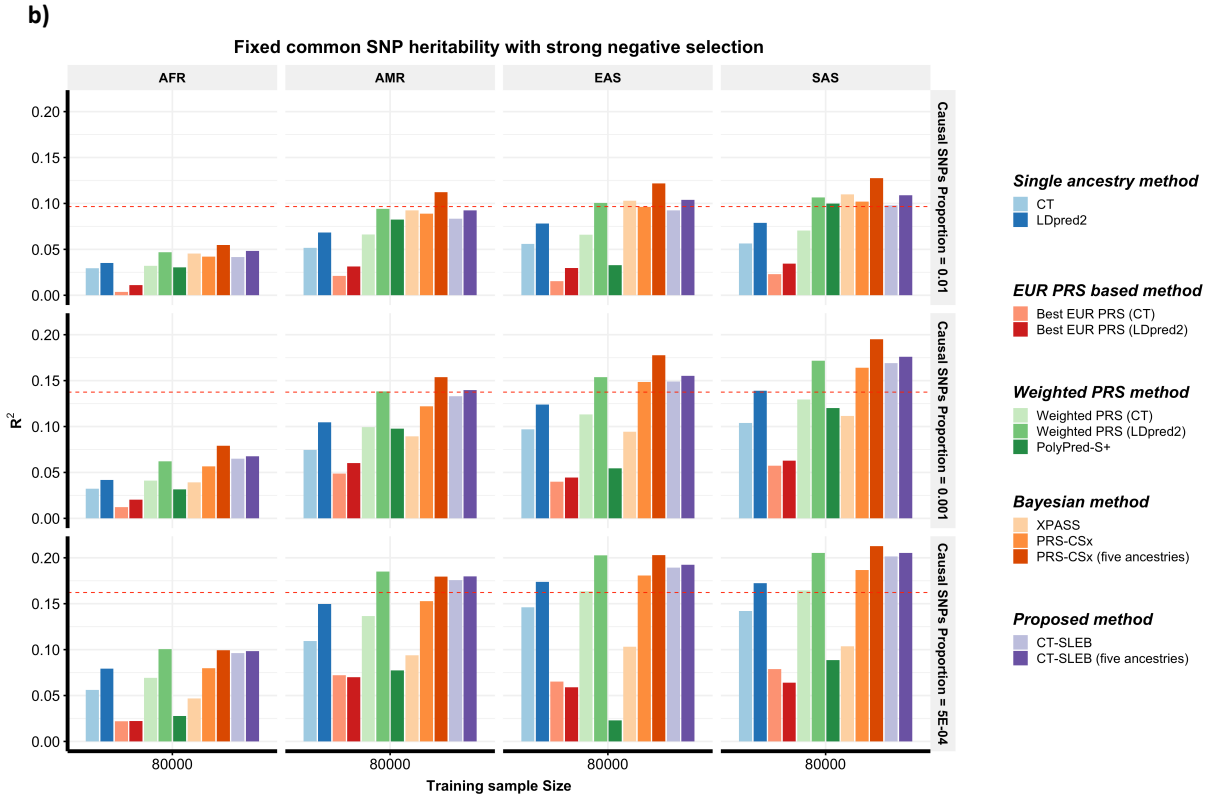

b)
Fixed common SNP heritability with strong negative selection
AFR
AMR
EAS
SAS
Causal SNPs Proportion = 0.01
Causal SNPs Proportion = 0.001
Causal SNPs Proportion = 5E-04
R2
0.20
0.15
0.10
0.05
0.00
80000
Training sample Size
Single ancestry method
CT
LDpred2
EUR PRS based method
Best EUR PRS (CT)
Best EUR PRS (LDpred2)
Weighted PRS method
Weighted PRS (CT)
Weighted PRS (LDpred2)
PolyPred-S+
Bayesian method
XPASS
PRS-CSx
PRS-CSx (five ancestries)
Proposed method
CT-SLEB
CT-SLEB (five ancestries)

Figure 3: Comparison of CT-SLEB PRS across different ancestries to single ancestry EUR PRS in the EUR population. The training sample size for each of the four non-EUR populations is 15,000, 45000, 80,000, or 100,000. The training sample size for the EUR population is fixed at 100,000, and PRS performance is evaluated using single ancestry CT or LDpred2, whichever performs the best in each setting. Two different genetic architectures are considered: either the common SNP heritability is fixed (at 0.4) (**Figure 3a and 3b**) or the per-SNP heritability is fixed (**Figure 3c and 3d**) across the five populations (**Figure 3c and 3d**). The effect-size correlation is assumed to be 0.8 across all pairs of populations. The effect sizes for causal variants are assumed to be related to allele frequency under a strong negative selection model. CT-SLEB uses the summary statistics from all five ancestries.

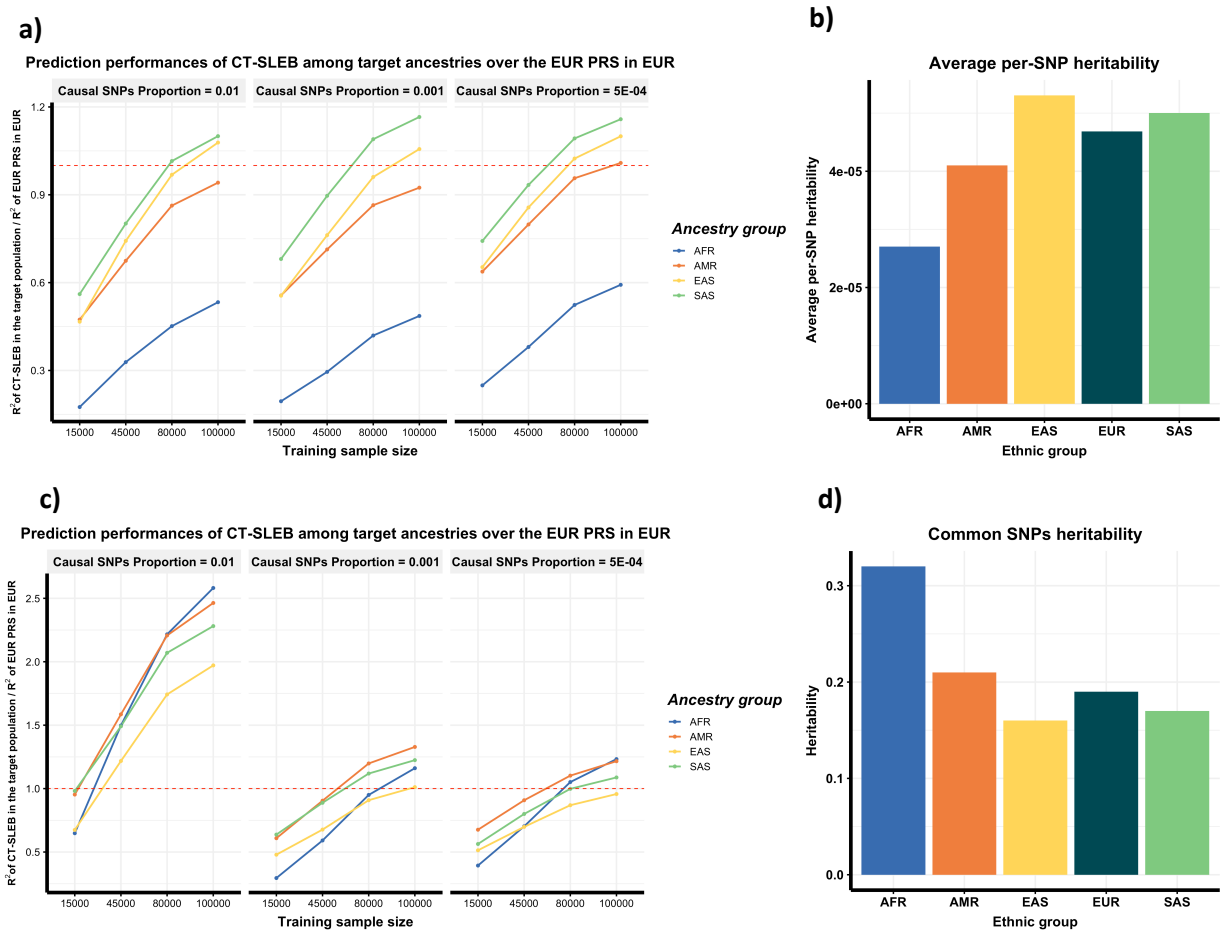


Figure 4: Prediction performance of CT-SLEB PRS under varying SNP densities. The analysis of each simulated data based on ~19 million SNPs is restricted to three different SNP sets: Hapmap3 (~1.3 million SNPs), Hapmap3 + Multi-Ethnic Genotyping Arrays (~2.0 million SNPs), 1000 Genomes Project (~19 million SNPs). The training sample size for each of the four non-EUR populations is 15,000 (**Figure 4a**) or 80,000 (**Figure 4b**). The training sample size for the EUR population is fixed at 100,000. Prediction R^2 values are reported based on independent validation dataset with 10,000 subjects per population. Common SNP heritability is assumed to be 0.4 across all populations, and effect-size correlation is assumed to be 0.8 across all pairs of populations. The proportion of causal SNPs proportion vary across 0.01 (top panel), 0.001 (medium panel), 5×10^{-4} (bottom panel), and effect sizes for causal variants are assumed to be related to allele frequency under a strong negative selection model.

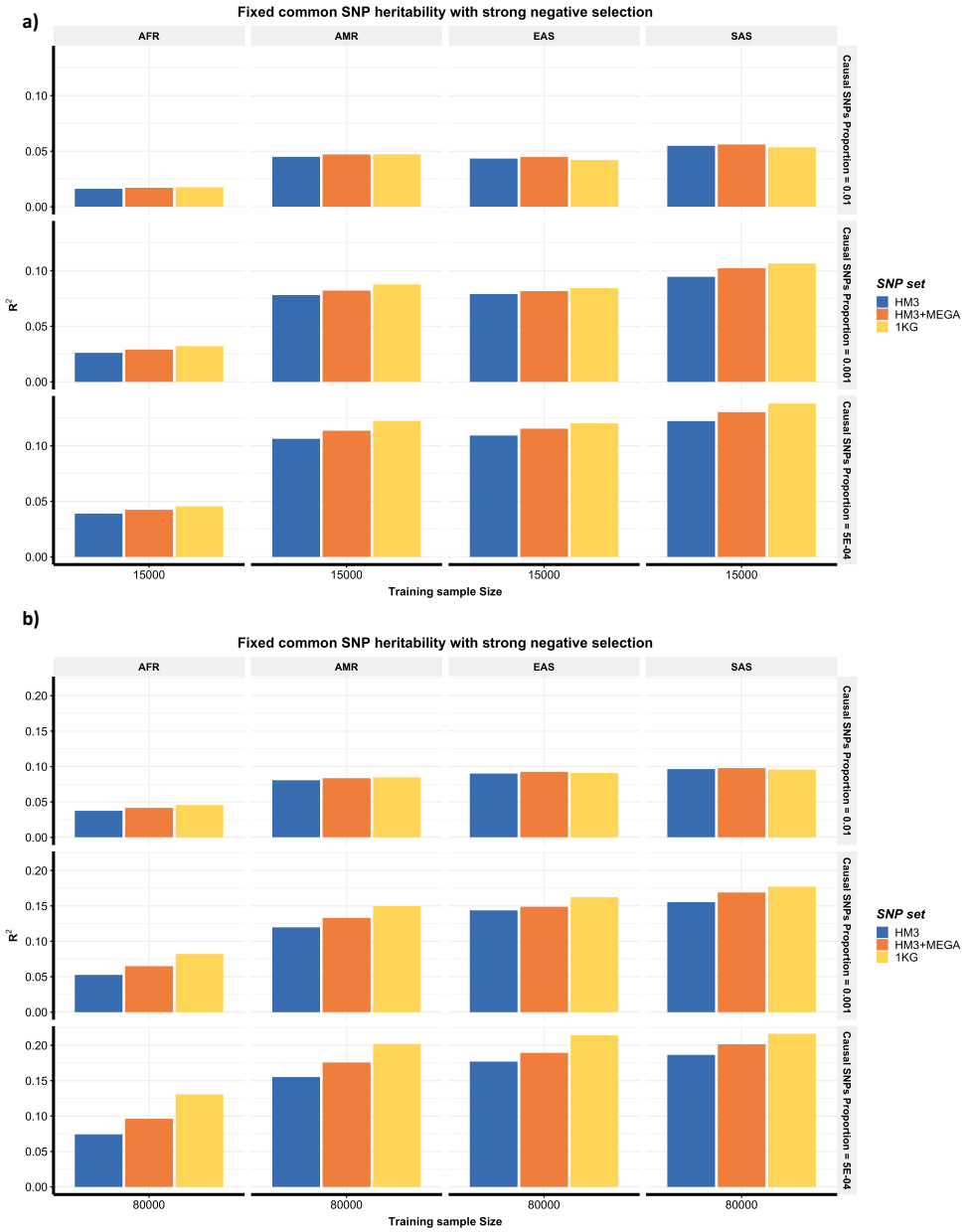


Figure 5: Prediction accuracy of PRSs for heart metabolic disease burden and height in 23andMe, Inc. datasets. The total sample size for heart metabolic disease burden and height is, respectively, 2.46 million and 2.93 million for European, 131K and 141K for African American, 375K and 509K for Latino, 110K and 121K for East Asian, and 29K and 32K for South Asian. The dataset is randomly split into 70%, 20%, 10% for training, tuning and validation dataset, respectively. The adjusted R^2 values are reported based on the performance of the PRS in the validation dataset, accounting for PC1-5, sex and age. The red dashed line represents the prediction performance of EUR PRS generated using single ancestry method (best of CT or LDpred2) in the EUR population. Analyses are restricted to ~2.0 million SNPs that are included in Hapmap3, or the Multi-Ethnic Genotyping Arrays chips array or both. PolyPred-S+ and PRS-CSx analyses are further restricted to ~1.3 million HM3 SNPs. All approaches are trained using data from the EUR and the target population. CT-SLEB and PRS-CSx are also evaluated using training data from five ancestries. From top to bottom panel, two continuous traits are displayed in the following order: 1. heart metabolic disease burden; 2. height.

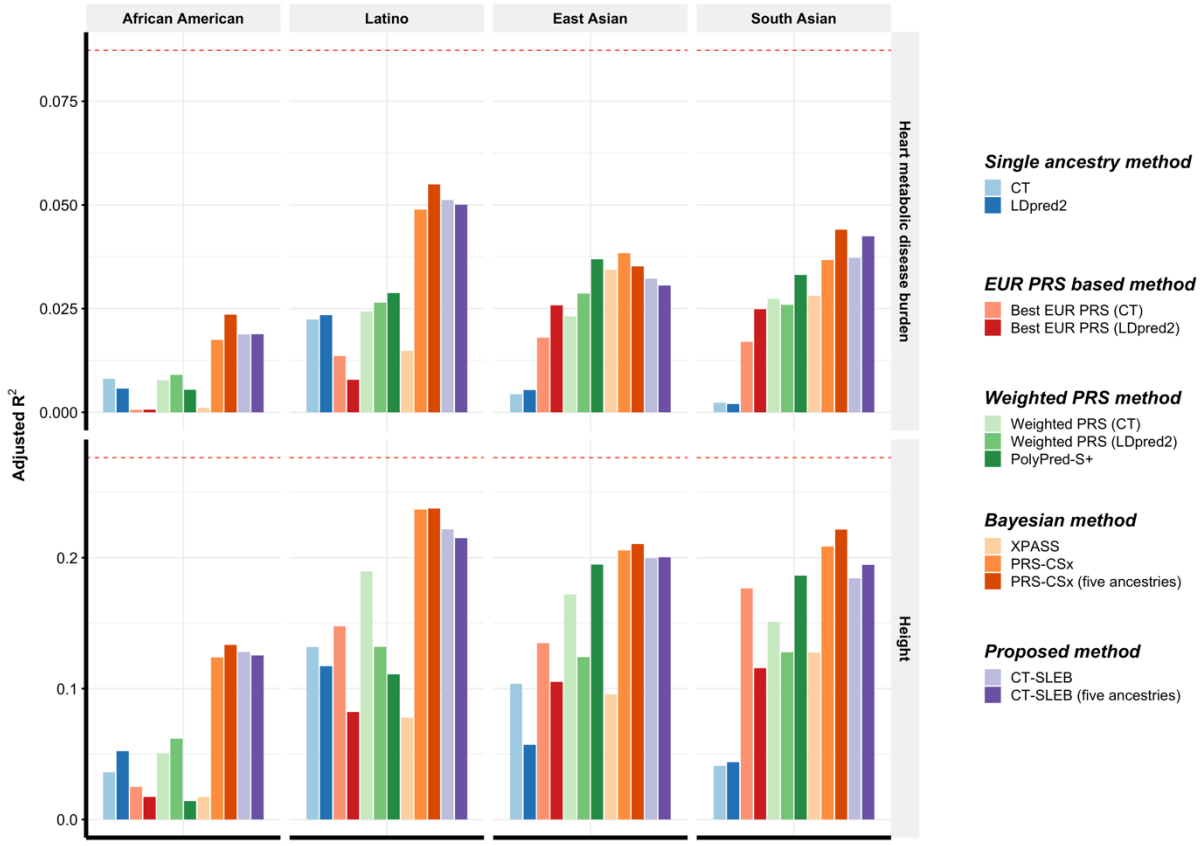


Figure 6: Prediction accuracy of five binary traits in 23andMe, Inc datasets. The data are from five populations: European (averaged N ≈ 2.37 million), African American (averaged N ≈ 109K), Latino (averaged N ≈ 401K), East Asian (averaged N≈ 86K), South Asian (averaged N≈ 24K). The datasets are randomly split into 70%, 20%, 10% for training, tuning and validation dataset, respectively. The adjusted AUC values are reported based on the validation dataset accounting for PC1-5, sex and age. The red dashed line represents the prediction performance of EUR PRS generated using single ancestry method (best of CT or LDpred2) in the EUR population. Analyses are restricted to ~2.0 million SNPs that are included in Hapmap3, or the Multi-Ethnic Genotyping Arrays chips array or both. PolyPred-S+ and PRS-CSx analyses are further restricted to ~1.3 million HM3 SNPs as implemented in the provided software. All approaches are trained using data from the EUR and the target population. CT-SLEB and PRS-CSx are also evaluated using training data from five ancestries. From top to bottom panel, five binary traits are displayed in the following order: 1.any cardiovascular disease (any CVD); 2. depression; 3. migraine diagnosis; 4. sing back musical note (SBMN); 5. morning person.

Figure 7: Prediction accuracy of four blood lipids traits from the Global Lipids Genetics Consortium. We used the GWAS summary statistics from five populations as the training data: European (N ≈ 931K), African (primarily African American, N ≈ 93K), Latino (N≈ 50K), East Asian (N ≈ $146K$), South Asian (N ≈ $34K$). The tuning and validation dataset are from UK Biobank data with three different ancestries African (N = 9,042), East Asian (N = 2,009), South Asian (N = 10,615). The tuning and validation are split with half and half. The adjusted R^2 values are reported based on the performance of the PRS in the validation dataset, while accounting for PC1-10, sex and age. The red dashed line represents the prediction performance of EUR PRS generated using single ancestry method (best of CT or LDpred2) in the EUR population. Analyses are restricted to ~2.0 million SNPs that are included in Hapmap3, or the Multi-Ethnic Genotyping Arrays chips array or both. PolyPred-S+ and PRS-CSx analyses are further restricted to ~1.3 million HM3 SNPs as has been implemented in the provided software. All approaches are trained using data from the EUR and the target population. CT-SLEB and PRS-CSx are also evaluated using training data from five ancestries. From top to bottom panel, four traits are displayed in the following order: 1. high-density lipoprotein cholesterol (HDL), 2. low-density lipoprotein cholesterol (LDL), 3. log triglycerides (logTG) and 4. total cholesterol (TC).

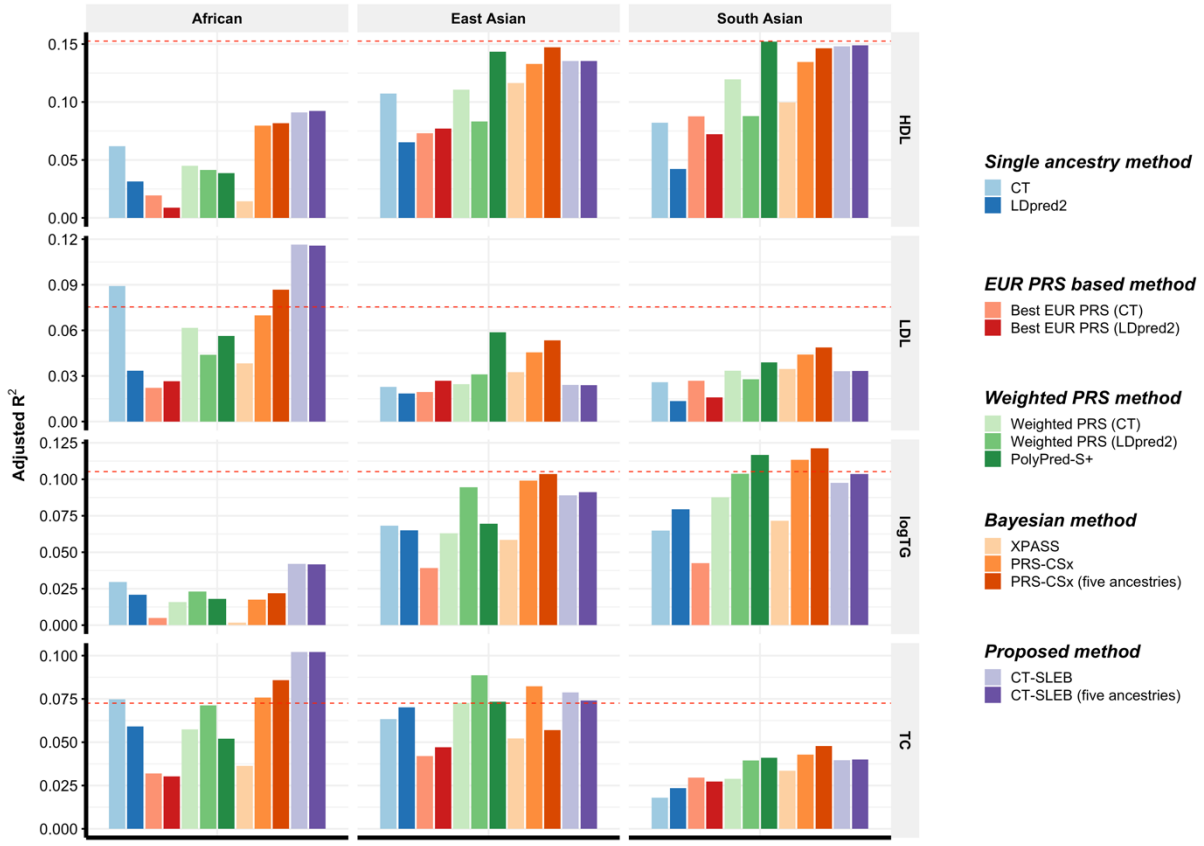
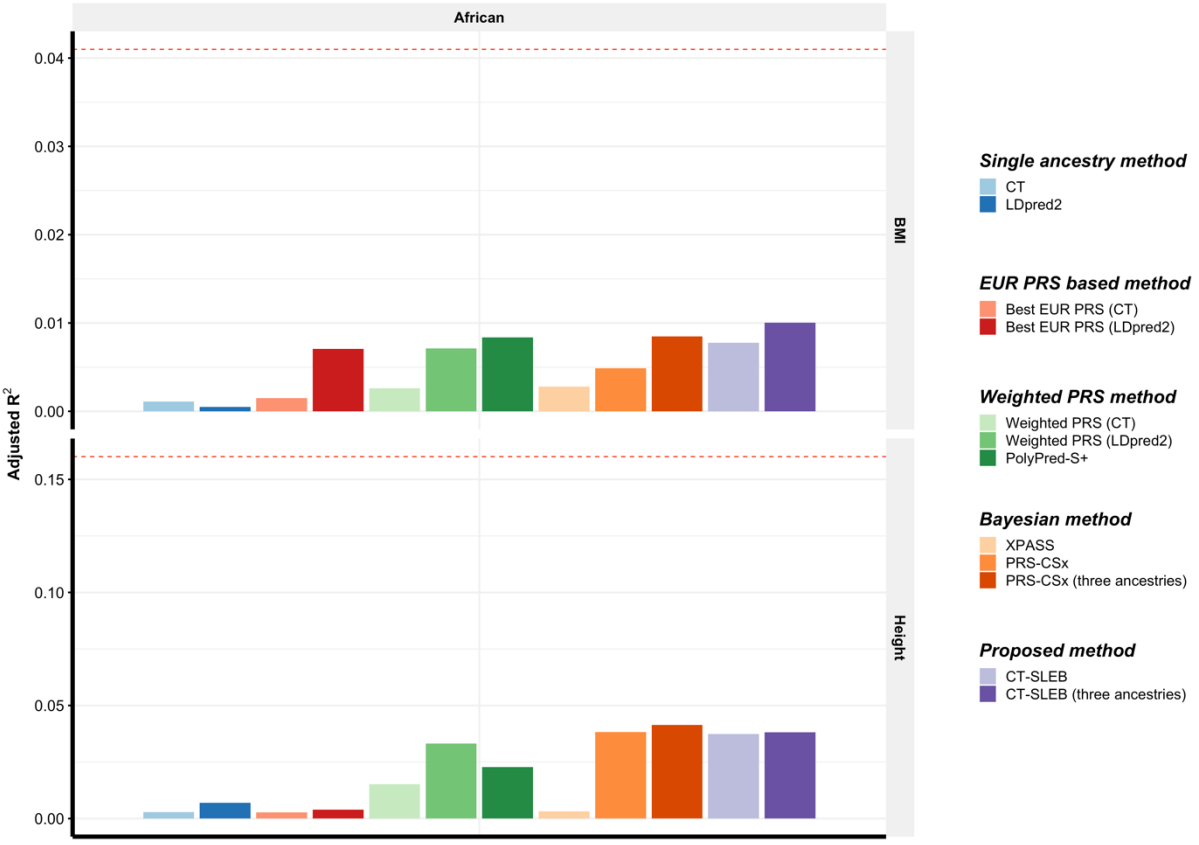



Figure 8: Prediction accuracy of two traits from All of Us dataset. We used the GWAS summary statistics from three populations as the training data: European (N ≈ 48K), African (N ≈ 22K), Latino (averaged N ≈ 15K). The tuning and validation dataset are from UK Biobank data with African (N = 9,042). The tuning and validation are split with half and half. The adjusted R^2 values are reported based on the performance of the PRS in the validation dataset, while accounting for PC1-10, sex and age. The red dashed line represents the prediction performance of EUR PRS generated using single ancestry method (best of CT or LDpred2) in the European population. Analyses are restricted to around 800K SNPs that are genotyped in All of Us dataset for different ancestries. All approaches are trained using data from the European and African population. CT-SLEB and PRS-CSx are further evaluated using training data from three ancestries: African, European and Latino. From top to bottom panel, two traits are displayed in the following order: 1. body mass index (BMI), and 2. height.