# A fast and robust Bayesian nonparametric method for prediction of complex traits using summary statistics

Geyu Zhou[1], Hongyu Zhao[1,2]

1. Program of Computational Biology and Bioinformatics, Yale University, New Haven, CT, United States of America.
2. Department of Biostatistics, Yale School of Public Health, New Haven, CT, United States of America.

Correspondence: hongyu.zhao@yale.edu

**Abstract**

Genetic prediction of complex traits has great promise for disease prevention, monitoring, and treatment. The development of accurate risk prediction models is hindered by the wide diversity of genetic architecture across different traits, limited access to individual level data for training and parameter tuning, and the demand for computational resources. To overcome the limitations of the most existing methods that make explicit assumptions on the underlying genetic architecture and need a separate validation data set for parameter tuning, we develop a summary statistics-based nonparametric method that does not rely on specific parametric assumptions about genetic architecture and validation datasets to tune parameters. In our implementation, we refine the commonly used likelihood assumption to deal with the discrepancy between summary statistics and external reference panel. We also leverage the block structure of the reference linkage disequilibrium matrix for implementation of a parallel algorithm. Through simulations and applications to twelve traits, we show that our method is adaptive to different genetic architectures, statistically robust, and computationally efficient. Our method is available at https://github.com/eldronzhou/SDPR.

## Introduction

Results from large-scale genome-wide association studies (GWAS) offer valuable information to predict personal traits based on genetic markers through polygenic risk scores (PRS) calculated from different methods. For one individual, PRS is typically calculated as the linear sum of the number of the risk alleles weighted by the effect size for each marker, such as single nucleotide polymorphism (SNP) [1]. PRS has gained great interest recently due to its demonstrated ability to identify individuals with higher disease risk for more effective prevention and monitoring [2].

Appropriate construction of PRS requires the development of statistical methods to jointly estimate the effect sizes of all genetic markers in an accurate and efficient way. Statistical challenges associated with the design of PRS methods largely reside in how to account for linkage disequilibrium (LD) among the markers and how to capture the genetic architecture of traits. Meanwhile, practical issues to be addressed include making use of summary statistics as input, as well as reducing the computational burden.

One simple method to compute PRS is to use a subset of SNPs in GWAS summary statistics formed by pruning out SNPs in LD and selecting those below a p value threshold (P+T) [1]. P+T is computationally efficient, though the prediction accuracy can usually be improved by using more sophisticated methods [3]. At present, most of the existing methods that allow the use of summary statistics as input assume a prior distribution on the effect sizes of the SNPs in the genome and fit the model under the Bayesian framework. Methods differ in the choice of the prior distribution. For example, LDpred assumes a point-normal mixture distribution or a single normal distribution [3, 4]. SBayesR assumes a mixture of three normal distributions with

a point mass at zero [5]. PRS-CS proposes a conceptually different class of continuous shrinkage priors [6]. In reality, there is wide diversity in the distribution of effect sizes for complex traits [7]. Therefore, there may be model specification for choosing a specific parametric prior if the true genetic architecture cannot be captured by the assumed parametric distribution. A natural solution is to consider a generalizable nonparametric prior, such as the Dirichlet process [8]. Dirichlet process regression (DPR) was shown to be adaptive to different parametric assumptions and could achieve robust performance when applied to different traits [9]. However, DPR requires access to individual-level genotype and phenotype data and has expensive computational cost when applied to large-scale GWAS data.

In this work, we derive a summary statistics-based method, called SDPR, which does not rely on specific parametric assumptions on the effect size distribution. SDPR connects the marginal coefficients in summary statistics with true effect sizes through Bayesian multiple Dirichlet process regression. We utilize the concept of approximately independent LD blocks and reparameterization to develop a parallel and fast-mixing Markov Chain Monte Carlo (MCMC) algorithm [10, 11]. Through simulations and real data applications, we demonstrate the advantages of our methods in terms of improved computational efficiency and more robust performance in prediction without the need of using a validation dataset to select tuning parameters.

## Methods

### Overview of SDPR

Suppose GWAS summary statistics are derived based on $N$ individuals and $p$ genetic markers, the phenotypes and genotypes can be related through a multivariate linear model,

$$y = X\beta + \epsilon \tag{1}$$

where $y$ is an $N \times 1$ vector of phenotypes, $X$ is an $N \times p$ matrix of genotypes, and $\beta$ is an $p \times 1$ vector of effect sizes. We further assume, without loss of generality, that both $y$ and columns of $X$ have been standardized. GWAS summary statistics usually contain the per SNP effect size $\hat{\beta}$ directly obtained or well approximated through the marginal regression $\hat{\beta} = \frac{X^T y}{N}$. Under the assumption that individual SNP explains relatively small percentage of phenotypic variance, the residual variance can be set to 1 and the likelihood function can be evaluated from

$$\hat{\beta}|\beta \sim N\left(R\beta, \frac{R}{N}\right) \tag{2}$$

where $R$ is the reference LD matrix [3, 12].

Like many Bayesian methods, we assume that the effect size of the i$^{th}$ SNP $\beta_i$, follows a normal distribution with mean 0 and variance $\sigma^2$. In contrast to methods assuming one particular parametric distribution, we consider placing a Dirichlet process prior on $\sigma^2$, i.e.

$$\beta_i \sim N(0, \sigma^2), \sigma^2 \sim DP(H, \alpha) \tag{3}$$

where $H$ is the base distribution and $\alpha$ is the concentration parameter controlling the shrinkage of the distribution on $\sigma^2$ toward $H$. To improve the mixing of MCMC and avoid the informativeness issue of inverse gamma distribution, we follow Gelman's advice to reparametrize the model and use the square of uniform distribution as the base distribution $H$ [13]. This is explained thoroughly in the supplementary note.

Dirichlet process has several equivalent probabilistic representations, of which stick-breaking process is commonly used for its convenience of model fitting [14]. The stick-breaking representation views the Dirichlet process as the infinite Gaussian mixture model

$$\beta_i \sim \sum_{k=1}^{\infty} p_k N(0, \sigma_k^2), \quad p_k = V_k \prod_{m=1}^{1-k} (1 - V_m), \quad V_k \sim Beta(1, \alpha), \sigma_k^2 \sim H \tag{4}$$

In practice, truncation needs to be applied so that the maximum number of components of the mixture model is finite. We found that setting the maximum components to 1000 was sufficient for our simulation and real data application because the number of non-trivial components, to which SNPs were assigned, was way fewer than 1000 (explained in the supplementary note). The first component of the mixture model is further fixed to 0 in analogous to Bayesian variable selection. We designed a parallel MCMC algorithm and implemented it in C++. The details of the algorithm can be found in the supplementary note.

**Robust design of the likelihood function**

Unlike individual-level data based methods, summary statistics based methods typically rely on external reference panel to estimate the LD matrix $R$. Ideally, the same set of individuals in the reference panel should be used to generate the summary statistics. However, due to the limited access to the individual level data of original GWAS studies, an external database with matched ancestry like the 1000 Genomes Project [15] or UK Biobank [16] is usually used instead to compute the reference LD matrix. It is possible that effect sizes of SNPs in summary statistics deviate from what are expected given the likelihood function and reference LD matrix, especially for SNPs in strong LD (Supplementary Table 1). This issue was also noted in the

section 5.5 of the RSS paper [12]. Failure to account for such discrepancy can cause severe model misspecification problems for SDPR and possibly other methods. Besides, double genomic control is applied to many summary statistics, which may lead to deflation of effect sizes [17, 18]. Thus, we design a robust likelihood function as follows in replace of commonly used equation (2).

$$\frac{\widehat{\beta}}{c}|\beta \sim N\left(R\beta, \frac{R + NaI}{N}\right) \tag{5}$$

More specifically, the input is divided by a constant provided by SumHer if application of double genomic control significantly deflates the effect sizes [17]. The covariance between two SNPs is shrunk toward 0 by introducing an additional parameter $a$. The connection between equation (5) and LDSC is discussed in the supplementary note. For simulated data, $c$ was set to 1 and $a$ was set to 0 since there was no above-mentioned discrepancy in simulation. In real data application, $Na$ was set to 0.1 and $c$ was set to 1 except for BMI (BMI $c = 0.74$ given by SumHer).

**Construction and partition of reference LD matrix**

We use an empirical Bayes shrinkage estimator to construct the LD matrix since the external reference panel like 1000G contains a limited number of individuals [19]. LD matrix can be divided into small "independent" blocks to allow for efficient update of posterior effect sizes using the blocked Gibbs sampler [6]. At present, ldetect is widely used for performing such tasks [10]. However, ldetect sometimes produces false positive partitions that violate the likelihood assumption of equation (3) (Supplementary Figure 1). To address this issue, we designed a simple and fast algorithm for partitioning independent blocks. The new algorithm

ensures that each SNP in one LD block does not have nonignorable correlation ($r^2 > 0.1$) with SNPs in other blocks so that the likelihood assumption of equation (3) is less likely to be violated (Supplementary Figure 1).

**Other methods**

We compared the performance of SDPR with four other methods: (1) PRS-CS as implemented in the PRS-CS software; (2) SBayesR as implemented in the GCTB software (version 2.02); (3) LDpred as implemented in the LDpred software (version 1.0.6); and (4) P+T as implemented in the PLINK software (version 1.90) [20]. We used the default parameter setting for all methods. For PRS-CS, the global shrinkage parameter was specified as 1e-6, 1e-4, 1e-2, 1 and auto. For SBayesR, gamma was specified as 0, 0.01, 0.1, 1 and pi was specified as 0.95, 0.02, 0.02, 0.01. For LDpred, the polygenicity parameter was specified as 1e-5, 3e-5, 1e-4, 3e-4, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3 ,1 (LDpred-Inf). For P+T, SNPs in GWAS summary statistics were clumped for $r^2$ iterated over 0.2, 0.4, 0.6, 0.8, and for p value threshold iterated over 5e-8, 5e-6, 1e-5, 1e-4, 5e-4, 1e-3, 1e-2, 0.04, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1. We tuned the parameters for PRS-CS, LDpred, and P+T using the validation dataset.

**Genome-wide simulations**

We used genotypes from UK Biobank to perform simulations. UK Biobank's database contains extensive phenotypic and genotypic data of over 500,000 individuals in the United Kingdom [16]. We selected 276,732 unrelated individuals of European ancestry based on data field 22021 and 22006. A subset of these individuals was randomly selected to form the training, validation and test datasets. Training datasets contained 10,000, 50,000, and 100,000

individuals, while validation and test datasets contained 10,000 individuals. We applied quality control (MAF > 0.05, genotype missing rate < 0.01, INFO > 0.3, pHWE > 1e-5) to select 4,458,556 SNPs from the original ~96 million SNPs. We then intersected these SNPs with 1000G HM3 SNPs (MAF > 0.05) and removed those in the MHC region (Chr6: 28-34 Mb) to form a set of 681,828 SNPs for simulation.

To cover a range of genetic architectures, we simulated effect sizes of SNPs under four scenarios: (1)-(3) $\beta_j \sim \pi N\left(0, \frac{h^2}{M\pi}\right) + (1-\pi)\delta_0$, where $h^2 = 0.5, M = 681828, \pi$ equaled $10^{-4}$ (scenario 1A), $10^{-3}$ (scenario 1B) and $10^{-2}$ (scenario 1C); (4) $\beta_j \sim \sum_{i=1}^{3} \pi_i N(0, c_i\sigma^2) + (1 - \sum_{i=1}^{3} \pi_i)\delta_0$ where $c = (1, 0.1, 0.01),\ \pi = (10^{-4}, 10^{-4}, 10^{-2})$. $\sigma^2$ was calculated so that the total heritability equaled 0.5. Importantly, scenario 1A-1C satisfied the assumption of LDpred, whereas scenario 4 satisfied the assumption of SBayesR. Phenotypes were generated from simulated effect sizes using GCTA-sim, and marginal linear regression was performed on the training data to obtain summary statistics using PLINK2 [21, 22]. In each scenario, we performed 10 simulation replicates.

We applied different methods on the training data, and used the 10,000 individuals in the validation dataset to estimate the LD matrix except for PRS-CS, which has the built-in LD matrix based on 503 EUR individuals in 1000G. Parameters for LDpred, P+T, and PRS-CS were also tuned using the validation data. We then evaluated the prediction performance on the test data by computing the square of Pearson correlation of PRS with simulated phenotypes.

**Real data application using public summary statistics and UK biobank data**

We obtained public GWAS summary statistics for 12 traits and evaluated the prediction performance of each method using the UK Biobank data. Individuals in GWAS do not overlap with individuals in UK Biobank. For this reason, we did not use the latest summary statistics of height and BMI [23]. To standardize the input summary statistics, we generally followed the guideline of LDHub to perform quality control on the GWAS summary statistics [24]. We removed strand ambiguous (A/T and G/C) SNPs, insertions and deletions (INDELs), SNPs with an effective sample size less than 0.67 times the $90^{th}$ percentile of sample size, and SNPs within the MHC region. For lipid traits, we further removed SNPs with extremely large effect sizes ($z^2 > 80$) to improve the convergence of MCMC. The remaining SNPs were then intersected with 1000G HM3 SNPs provided in the PRS-CS reference panel. Table 1 shows the number of SNPs present in the summary statistics for each trait after performing quality control.

For UK Biobank, we first selected unrelated European individuals as we did in simulations. We then applied quality control (MAF > 0.01, genotype missing rate < 0.05, INFO > 0.8, pHWE > 1e-10) to obtain a total of 1,114,176 HM3 SNPs. UK Biobank participants with six quantitative traits-height, body mass index (BMI), high-density lipoproteins (HDL), low-density lipoproteins (LDL), total cholesterol, and triglycerides-were selected based on relevant data fields (Supplementary Note). Selected participants were randomly assigned to form validation and test datasets, each composing half of the individuals. Cases for each of six diseases-coronary artery diseases, breast cancer, inflammatory bowel disease (IBD), type 2 diabetes, bipolar, and schizophrenia-were selected based on self-reported questionnaire and ICD code in the electronic hospital record (EHR). Controls were selected among participants in the EHR based on certain exclusion criteria (Supplementary Note). Validation dataset consisted of an

equal number of cases and controls, the rest of which were assigned to the test dataset (Table 1). Random assignments of individuals to validation and test datasets were repeated for 10 times.

For six quantitative traits, we reported the prediction $R^2$ of PRS (variance explained by PRS) defined as $R^2 = 1 - \frac{SS_1}{SS_0}$, where $SS_0$ is the sum of squares of the residuals of the restricted linear regression model with covariates (an intercept, age, sex, top 10 PCs of the genotype data), and $SS_1$ is the sum of squares of the residuals of the full linear regression model (covariates above and PRS). For six diseases, we reported the Nagelkerke's $R^2$ and AUC. Nagelkerke's $R^2$ is defined as $R^2 = \frac{1-\left(\frac{L_0}{L_1}\right)^{2/N}}{1-L_0^{2/N}}$, where $N$ is the sample size of the testing dataset, $L_0$ is the likelihood of the restricted logistic regression model with covariates, and $L_1$is the likelihood of the full logistic regression model (covariates and PRS).

**Code availability**

SDPR is available on https://github.com/eldronzhou/SDPR under the GPLv3 license. The scripts used for analysis in this paper are available on https://github.com/eldronzhou/SDPR_paper.

**Data availability**

UK Biobank data are available to registered investigations under approved applications. All GWAS summary statistics are publicly available and can be downloaded from the website of consortiums.

## Results

### Simulations

We first compared the performance of SDPR with several other summary statistics-based methods using simulations across different genetic architectures and training sample sizes. Effect sizes of SNPs were simulated under a point-normal mixture model with increasing number of causal variants, and a point-three-normal mixture model satisfying SBayesR's assumption (details in methods). The heritability was fixed as 0.5 and 10 replicates were performed in each simulation setting. Tuning parameters of PRS-CS, LDpred and P+T were selected using a validation dataset (N = 10,000). 10,000 individuals in the validation dataset were used to construct the LD matrix except for PRS-CS, which has a built-in LD matrix based on 503 EUR individuals in 1000G. We evaluated the prediction performance on the independent test data (N = 10,000) using the squared Pearson correlation coefficient ($R^2$). We also reported the difference of $R^2$ between our method and other methods.

The prediction accuracy of all methods generally increased along the sample size of training data (Figure 1; Supplementary Table 2-5). Similarly, all methods performed better when the number of causal variants was small. Since the standard error of the regression coefficient estimator in GWAS summary statistics is roughly reciprocal to the square root of the sample size of the training cohort, the dominance of noise over signal poses significant challenges for accurate estimation of effect sizes when the training sample size or per SNP effect size is small.

Overall, SDPR and SBayesR performed better than other methods across all simulation scenarios (Figure 1; Supplementary Table 2-5). Consistent with others' findings, we observed

that when the genetic architecture was sparse, the performance of LDpred decreased as the training sample size increased[6]. Meanwhile, PRS-CS performed worse than LDpred when the training sample size was small. The suboptimal performance of PRS-CS might be attributed to the difference regarding the choice and partition of the reference LD matrix. In contrast, SDPR and SBayesR were more robust to the change of genetic architecture and the training sample size, demonstrating the advantage of using a mixture of point mass and multiple normal distributions as the prior of effect sizes.

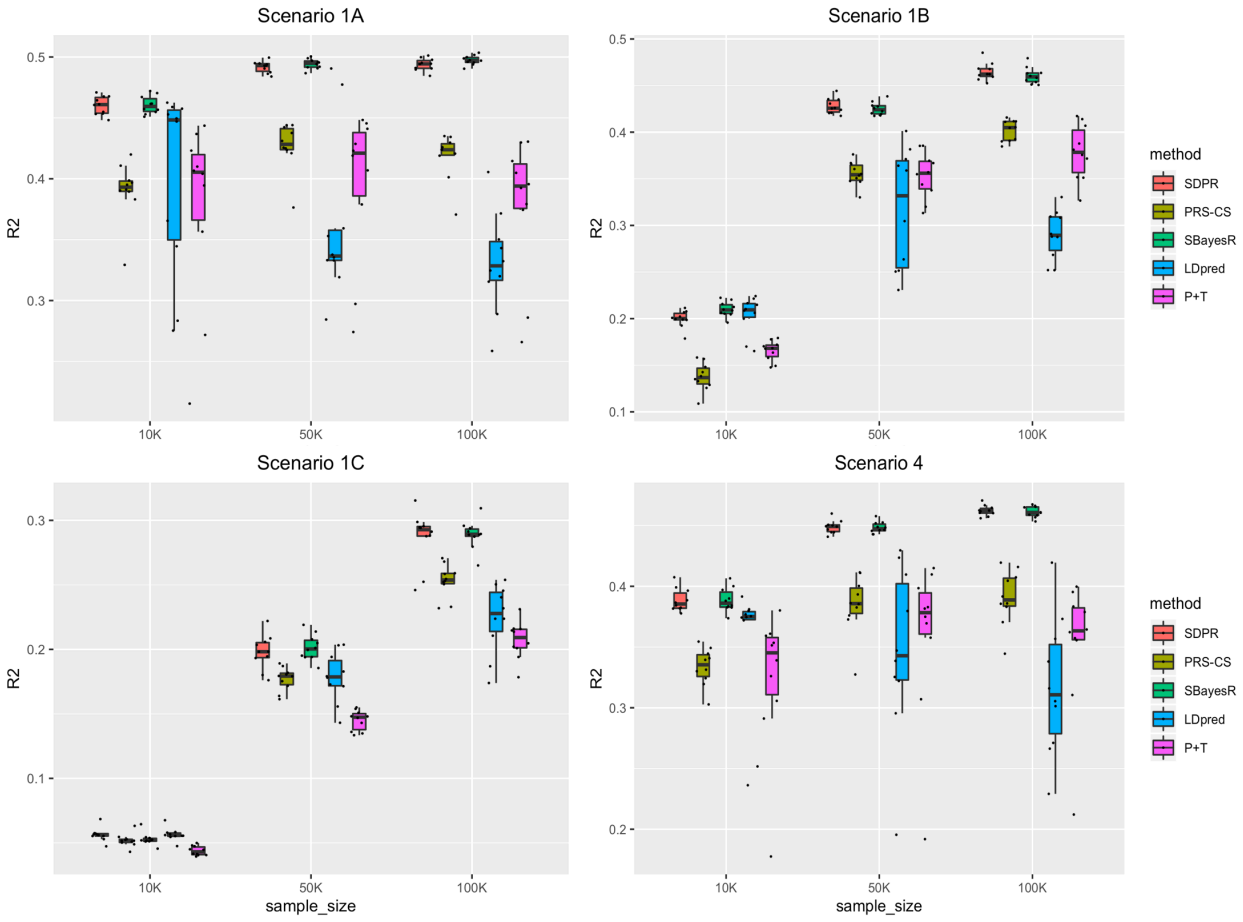


Figure 1. Prediction performance of different methods on simulated data with varying samples sizes of the training cohort. Scenarios 1A-1C: mixture of Dirichlet delta and normal distribution (spike and slab) with number of causal SNPs increasing from 100, 1000 to 10000. Scenario 4: mixture of Dirichlet delta

and three normal distributions. The total heritability in all scenarios was fixed to 0.5. Simulation in each scenario was repeated for 10 times. For each boxplot, the central mark is the median and the lower and upper edges represents the 25$^{th}$ and 75$^{th}$ percentile. The median is recorded in the supplementary table 2-5.

**Real data applications**

We compared the performance of SDPR with other methods in real datasets to predict six quantitative traits (height, body mass index, high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides) and six diseases (coronary artery diseases, breast cancer, inflammatory bowel disease, type 2 diabetes, bipolar, and schizophrenia) in UK Biobank. We obtained public GWAS summary statistics of these traits and performed quality control to standardize the input (details in Methods; Table 1). A total of 503 1000G EUR individuals were used to construct the reference LD matrix for SDPR, PRS-CS, LDpred and P+T. For SBayesR, we used 5000 EUR individuals in UK Biobank to create the LD matrix (shrunken and sparse) instead, as it was reported to have suboptimal prediction accuracy when using 1000G samples [5].

| Trait | GWAS sample size | GWAS ref | 1KG HM3 & UKB & GWAS SNPs | UKB validation Sample size | UKB testing sample size |
|---|---|---|---|---|---|
| Height | 252,230 | [25] | 885,791 | 138,066 | 138,066 |
| BMI | 233,766 | [26] | 886,654 | 137,921 | 137,920 |
| HDL | 94,288 | [27] | 868,140 | 37,774 | 37,774 |
| LDL | 89,866 | [27] | 867,754 | 40,807 | 40,807 |
| Total Cholesterol | 94,571 | [27] | 868,134 | 40,898 | 40,898 |
| Triglycerides | 90,989 | [27] | 867,752 | 40,858 | 40,857 |
| Coronary artery disease | 61,294 (22,233/64,762) | [28] | 814,337 | 4475/4475 | 4475/258,345 |
| Breast Cancer | 227,688 (122,977/105,974) | [29] | 927,706 | 4539/4539 | 4539/133,649 |

| | | | | | |
|---|---|---|---|---|---|
| Inflammatory bowel disease | 32,372 (12,882/21770) | [30] | 917,367 | 1840/1840 | 1839/198,815 |
| Type 2 diabetes | 156,109 (26,676/132,532) | [31] | 974,907 | 7240/7240 | 7239/182,292 |
| Bipolar | 41,606 (20,129/21,524) | [32] | 928,032 | 832/832 | 832/176,069 |
| Schizophrenia | 65,955 (33,426/32541) | [32] | 941,216 | 223/223 | 223/203,471 |

Table 1. Summary information about the sample size and SNPs in GWAS summary statistics and UK Biobank datasets. For binary traits, effective sample size was used ($\frac{4*N_{case}*N_{control}}{N_{case}+N_{control}}$) and the validation datasets consisted of equal numbers of cases and controls. If the summary statistics included sample sizes for individual SNPs, the median of all SNPs passing QC was reported. For binary traits, the number of cases and controls were reported in the parenthesis.

For six continuous traits, the prediction performance was measured by variance of phenotype explained by PRS (Figure 2; Supplementary Table 6). Overall, SDPR showed robust performance across these traits. For height and HDL, SDPR and PRS-CS performed similarly and better than other methods. SDPR performed best for BMI, LDL and total cholesterol, while PRS-CS performed best for triglycerides. We observed convergence issues when running SBayesR on these traits, and followed its manual to filter SNPs based on GWAS P-values and LD R-squared (--p-value 0.4 --rsq 0.9). The filtering approach improved the prediction performance of SBayesR, but it still failed to achieve comparable performance with SDPR and PRS-CS. We suspect that the convergence issue of SBayesR was also caused by the violation of the likelihood assumption for SNPs in extreme LD (details in Methods). To address this issue, our approach of modifying the likelihood function might be better than the simple filtering approach used in SBayesR and P+T as it retained all SNPs for prediction.

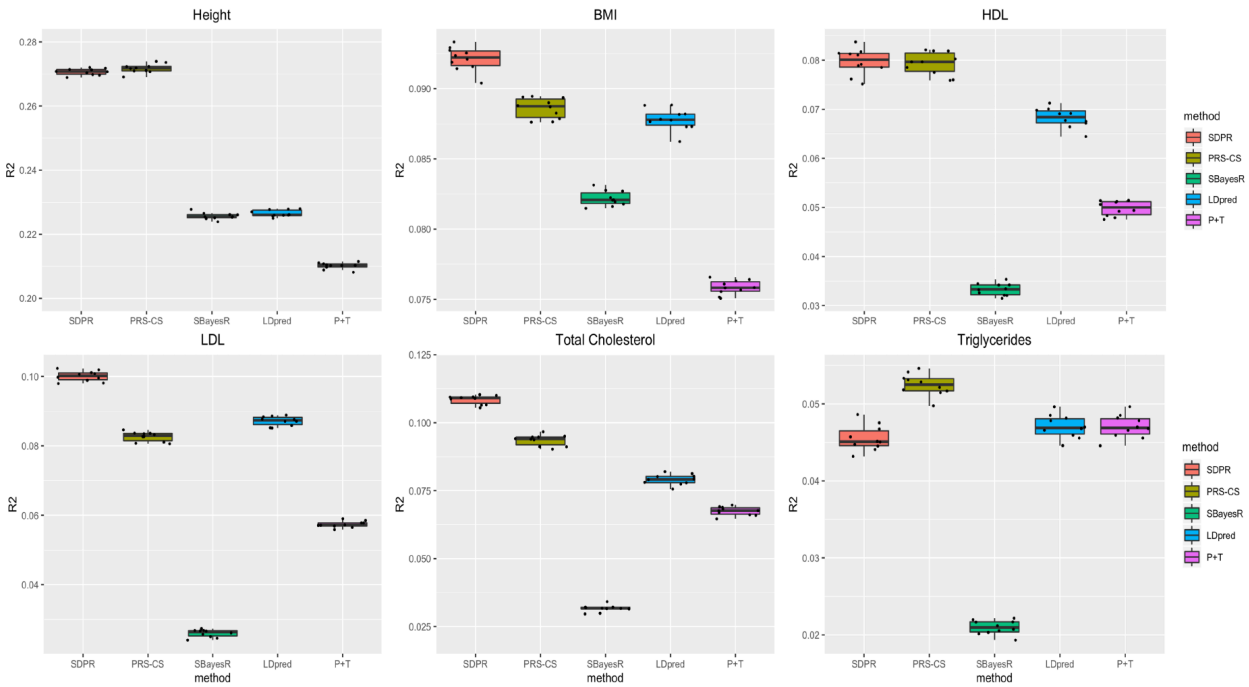


Figure 2. Prediction performance of different methods for six quantitative traits in the UK Biobank. Selected participants with corresponding phenotypes were randomly assigned to form validation and test dataset, each composing half of individuals. For PRS-CS, LDpred and P+T, parameters were tuned based on the performance on the validation dataset. We repeated the split and tuning process 10 times. The median of variance of phenotypes explained by PRS across 10 random splits was reported in the supplementary table 6.

For six disease traits, the prediction performance was measured by Nagelkerke's $R^2$ and AUC (Figure 3 and Supplementary Figure 3; Supplementary Table 7-8). LDpred performed best for coronary artery disease. SDPR and PRS-CS performed best for breast cancer. For schizophrenia and type 2 diabetes, SDPR and SBayesR performed best. LDpred, SDPR and SBayesR performed better for IBD. All methods performed similarly for bipolar. Overall, SDPR

was robust as it achieved top-tier performance for five diseases. In contrast, PRS-CS had suboptimal performance for type 2 diabetes and schizophrenia, while SBayesR underperformed for coronary artery disease and breast cancer. LDpred did not perform well for type 2 diabetes, breast cancer and schizophrenia.

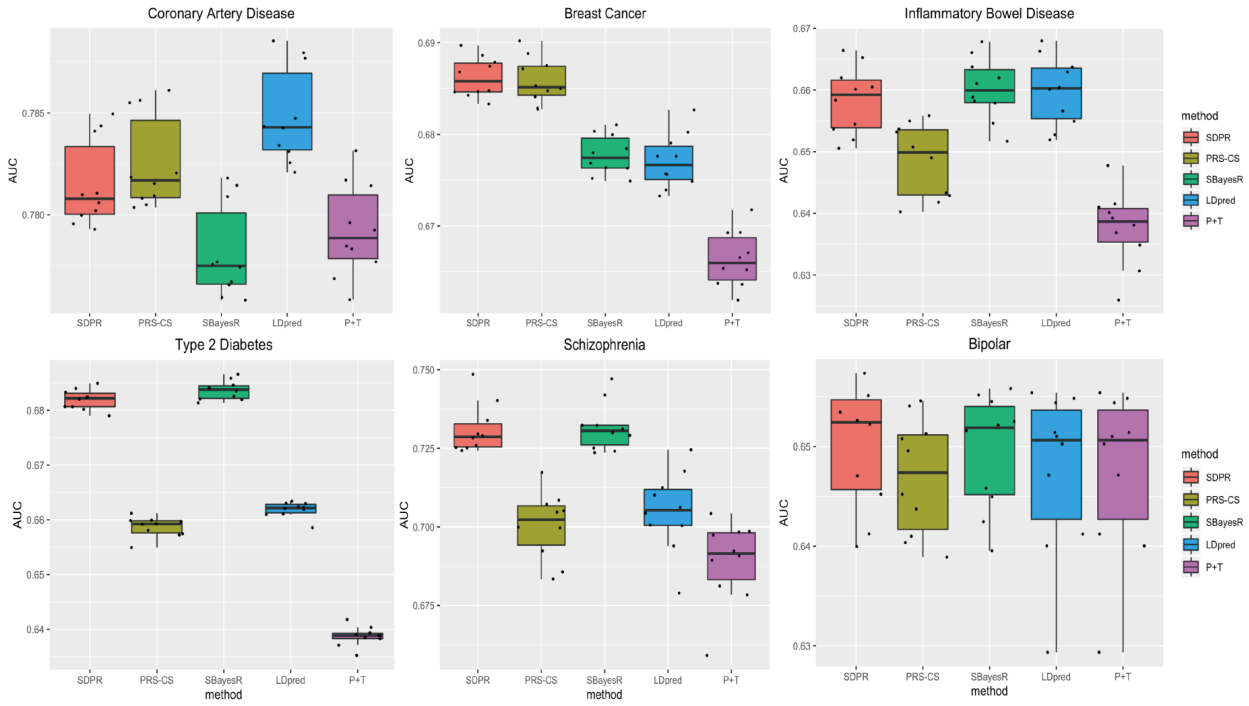


Figure 3. Prediction performance of different methods for 6 diseases in the UK biobank. Selected participants with corresponding diseases were randomly assigned to form validation and test dataset (Table 1). For PRS-CS, LDpred and P+T, parameters were tuned based on the performance on the validation dataset. We repeated the split and tuning process for 10 times. The median AUC across 10 random splits was reported in the supplementary table 7.

Consistent with simulations, SBayesR performed similarly to SDPR when there was no convergence issue (IBD, type 2 diabetes, schizophrenia, bipolar vs height, lipid traits). In general, PRS-CS performed better when the training sample size was large (height and breast

cancer vs IBD and type 2 diabetes) and LDpred performed better when the training sample size was small (coronary artery disease, IBD vs height, breast cancer). Taken together, our design of the likelihood function and usage of Dirichlet process prior empowers SDPR with generally robust performance across different genetic architectures and training sample sizes.

**Computational time**

SDPR is implemented in C++ to best utilize the resources of high-performance computing facilities. SDPR optimizes the speed of the computational bottleneck by using SIMD programming, parallelization over independent LD blocks, and high-performance linear algebra library. Besides, SDPR by default runs analysis on each chromosome in parallel because the genetic architecture may be different across chromosomes. We benchmarked the computational time and memory usage of each method on an Intel Xeon Gold 6240 processor (2.60 GHZ). For SDPR and PRS-CS, we paralleled computation over 22 chromosomes and used three threads per chromosome for Intel® MKL® (22 ×3 = 66 threads in total). Time and memory usage were reported for the longest chromosome, which was the rate limiting step. For LDpred, SBayesR and P+T, no parallelization was used. The evaluation was based on a fixed number of MCMC iterations-1000 for SDPR and PRS-CS (default), 4000 for SBayesR (non-default but achieved generally good performance in simulations and real data application), 100 for LDpred (default). One should keep in mind that the number of iterations affects the computation time significantly, though we did not explore it in this paper since each method also has different convergence properties.

Table 3 shows that SDPR was able to finish the analysis in 15 minutes for most traits and required no more than 3 Gb of memory for each chromosome. SBayesR was also fast but the memory usage was significant for five diseases as no SNPs were removed to improve the convergence. The speed of PRS-CS and LDpred was impeded by the need of iterating over tuning parameters. PRS-CS used less memory because the largest size of LD blocks output by ldetect was smaller compared with SDPR. The speed of P+T was hampered by iterating over tuning parameters to compute PRS in the validation and testing datasets, which contained a large number of individuals.

| Trait | SDPR | PRS-CS | SBayesR | LDpred | P+T |
|---|---|---|---|---|---|
| Height | 0.20 (2.4) | 2.5 (0.7) | 0.92 (12.6) | 5.0 (15.5) | 3.3 (0.1) |
| BMI | 0.18 (2.4) | 2.8 (0.7) | 0.50 (7.6) | 4.9 (15.1) | 3.0 (0.1) |
| HDL | 0.20 (2.4) | 1.6 (0.7) | 0.68 (8.5) | 5.1 (15.6) | 3.5 (0.1) |
| LDL | 0.22 (2.4) | 2.2 (0.7) | 0.67 (8.7) | 5.1 (15.6) | 3.6 (0.1) |
| Total cholesterol | 0.25 (2.4) | 2.2 (0.7) | 0.48 (8.7) | 5.1 (15.4) | 3.5 (0.1) |
| Triglycerides | 0.21 (2.4) | 2.2 (0.7) | 0.50 (8.3) | 5.1 (15.5) | 3.5 (0.1) |
| Coronary artery disease | 0.23 (2.3) | 1.9 (0.7) | 0.39 (7.0) | 4.7 (14.0) | 3.3 (0.1) |
| Breast cancer | 0.20 (2.9) | 2.7 (0.7) | 0.63 (42.3) | 5.5 (16.4) | 3.2 (0.1) |
| IBD | 0.28 (2.8) | 2.2 (0.7) | 0.78 (39.5) | 5.1 (16.0) | 3.6 (0.1) |
| Type 2 diabetes | 0.31 (2.9) | 2.4 (0.7) | 0.87 (47.4) | 5.5 (17.4) | 3.5 (0.1) |
| Schizophrenia | 0.28 (2.7) | 2.3 (0.7) | 2.6 (42.1) | 5.3 (16.4) | 2.9 (0.1) |
| Bipolar | 0.28 (2.8) | 2.2 (0.7) | 1.7 (43.8) | 5.3 (16.3) | 2.5 (0.1) |

Table 3. Computational time and memory usage of different methods for 12 traits. The computational time is in hours. Memory usage of each method, as listed in the parenthesis, is measured in the unit of Gigabytes (Gb). We did not include the time of computing PRS in the validation and test datasets except for P+T, because such computation was a rate limiting step only for P+T.

## Discussion

Building on the success of genome wide association studies, polygenic prediction of complex traits has shown great promise with both public health and clinical relevance. Recently, there is growing interest in developing non-parametric or semi-parametric approaches that make minimal assumptions about the distribution of effect sizes to improve genetic risk prediction [9, 33, 34]. However, these methods either require external training datasets or do no account for LD. Other widely used methods usually make specific parametric assumptions, and require external validation or pseudo-validation datasets to optimize the prediction performance [3, 6, 35]. To address the limitations of the existing methods, we have proposed a non-parametric method SDPR that is adaptive to different genetic architectures, statistically robust, and computationally efficient. Through simulations and real data applications, we have illustrated that SDPR is practically simple, fast yet effective to achieve competitive performance. Although we have focused on the polygenic prediction of SDPR in this paper, it can provide estimation of heritability, genetic architecture, and posterior inclusion probability (PIP) for fine mapping. These issues will be fully explored in our future studies. SDPR can also be extended as a summary statistics-based tool to predict gene expression level for transcriptome wide association studies since a previous study has shown that individual level data based Dirichlet process model improves transcriptomic data imputation [36].

Although our method has robust performance in comparison with other methods, we caution that currently for most traits the prediction accuracy is still limited for direct application in clinical settings. From our perspective, there are three factors that affect the prediction accuracy. First, how much heritability is explained by common SNPs for diseases and complex traits? Second, if diseases or complex traits have relatively moderate heritability, is the GWAS

sample size large enough to allow accurate estimation of effect sizes? Third, if the above two conditions are met, is a method able to have good prediction performance? The first two questions have been discussed in the literatures [7, 37, 38]. As for method development, we have focused on addressing the third question in this paper, and think SDPR represents a solid step in polygenic risk prediction.

Finally, we provide two technical directions for further development of SDPR. First, SDPR may have better performance after incorporating functional annotation as methods utilizing functional annotation generally perform better [39]. Second, studies have shown that PRS developed using EUR GWAS summary statistics does not transfer well to other populations[40]. We can further modify the likelihood function to account for different LD patterns across populations to improve the performance of trans-ethnic PRS.

## Acknowledgements

This study was supported in part by NIH grant NIH GM 134005 and NSF grants DMS 1713120 and 1902903 (G.Z. and H.Z.); the Yale World Scholars Program sponsored by the China Scholarship Council (G.Z.). We conducted the research using the UK Biobank resource under an approved data request (ref: 29900). We sincerely thank many GWAS consortia for making their GWAS summary data publicly accessible.

## Author contributions

G.Z. and H.Z. conceptualized the study. G.Z. curated the data, developed the method, implemented the software, and performed the analysis. H.Z. provided statistical guidance. G.Z. and H.Z. wrote the manuscript.

## References


1. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460(7256):748-52. Epub 2009/07/03. doi: 10.1038/nature08185. PubMed PMID: 19571811; PubMed Central PMCID: PMCPmc3912837.
2. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219-24. Epub 2018/08/15. doi: 10.1038/s41588-018-0183-z. PubMed PMID: 30104762; PubMed Central PMCID: PMCPmc6128408.
3. Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. American journal of human genetics. 2015;97(4):576-92. Epub 2015/10/03. doi: 10.1016/j.ajhg.2015.09.001. PubMed PMID: 26430803; PubMed Central PMCID: PMCPmc4596916.
4. Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. bioRxiv. 2020:2020.04.28.066720. doi: 10.1101/2020.04.28.066720.
5. Lloyd-Jones LR, Zeng J, Sidorenko J, Yengo L, Moser G, Kemper KE, et al. Improved polygenic prediction by Bayesian multiple regression on summary statistics. Nature communications. 2019;10(1):5086. doi: 10.1038/s41467-019-12653-0.
6. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nature communications. 2019;10(1):1776. Epub 2019/04/18. doi: 10.1038/s41467-019-09718-5. PubMed PMID: 30992449; PubMed Central PMCID: PMCPMC6467998.
7. Zhang Y, Qi G, Park J-H, Chatterjee N. Estimation of complex effect-size distributions using summary-level statistics from genome-wide association studies across 32 complex traits. Nature Genetics. 2018. doi: 10.1038/s41588-018-0193-x.
8. Ferguson TS. A Bayesian Analysis of Some Nonparametric Problems. Ann Statist. 1973;1(2):209-30. doi: 10.1214/aos/1176342360.
9. Zeng P, Zhou X. Non-parametric genetic prediction of complex traits with latent Dirichlet process regression models. Nature communications. 2017;8(1):456. Epub 2017/09/08. doi: 10.1038/s41467-017-00470-2. PubMed PMID: 28878256; PubMed Central PMCID: PMCPmc5587666.
10. Berisa T, Pickrell JK. Approximately independent linkage disequilibrium blocks in human populations. Bioinformatics. 2016;32(2):283-5. Epub 2015/09/24. doi:

10.1093/bioinformatics/btv546. PubMed PMID: 26395773; PubMed Central PMCID: PMCPmc4731402.
11. Gelman A, van Dyk DA, Huang Z, Boscardin JW. Using Redundant Parameterizations to Fit Hierarchical Models. Journal of Computational and Graphical Statistics. 2008;17(1):95-122. doi: 10.1198/106186008X287337.
12. Zhu X, Stephens M. BAYESIAN LARGE-SCALE MULTIPLE REGRESSION WITH SUMMARY STATISTICS FROM GENOME-WIDE ASSOCIATION STUDIES. Ann Appl Stat. 2017;11(3):1561-92. Epub 2018/02/06. PubMed PMID: 29399241; PubMed Central PMCID: PMCPmc5796536.
13. Gelman A. Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). Bayesian Anal. 2006;1(3):515-34. doi: 10.1214/06-BA117A.
14. Ishwaran H, James LF. Gibbs Sampling Methods for Stick-Breaking Priors. Journal of the American Statistical Association. 2001;96(453):161-73. doi: 10.1198/016214501750332758.
15. Auton A, Abecasis GR, Altshuler DM, Durbin RM, Abecasis GR, Bentley DR, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68-74. doi: 10.1038/nature15393.
16. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-9. Epub 2018/10/12. doi: 10.1038/s41586-018-0579-z. PubMed PMID: 30305743.
17. Speed D, Balding DJ. SumHer better estimates the SNP heritability of complex traits from summary statistics. Nat Genet. 2019;51(2):277-84. Epub 2018/12/05. doi: 10.1038/s41588-018-0279-5. PubMed PMID: 30510236; PubMed Central PMCID: PMCPMC6485398.
18. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999;55(4):997-1004. Epub 2001/04/21. doi: 10.1111/j.0006-341x.1999.00997.x. PubMed PMID: 11315092.
19. Schafer J, Strimmer K. A shrinkage approach to large-scale covariance matrix estimation and implications for functional genomics. Statistical applications in genetics and molecular biology. 2005;4:Article32. Epub 2006/05/02. doi: 10.2202/1544-6115.1175. PubMed PMID: 16646851.
20. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. American journal of human genetics. 2007;81(3):559-75. Epub 2007/08/19. doi: 10.1086/519795. PubMed PMID: 17701901; PubMed Central PMCID: PMCPMC1950838.
21. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. American journal of human genetics. 2011;88(1):76-82. Epub 2010/12/21. doi: 10.1016/j.ajhg.2010.11.011. PubMed PMID: 21167468; PubMed Central PMCID: PMCPmc3014363.
22. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience. 2015;4:7. Epub 2015/02/28. doi: 10.1186/s13742-015-0047-8. PubMed PMID: 25722852; PubMed Central PMCID: PMCPMC4342193.
23. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in ∼700000 individuals of European ancestry. Hum Mol Genet. 2018;27(20):3641-9. Epub 2018/08/21. doi: 10.1093/hmg/ddy271. PubMed PMID: 30124842; PubMed Central PMCID: PMCPMC6488973.

24. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33(2):272-9. Epub 2016/11/03. doi: 10.1093/bioinformatics/btw613. PubMed PMID: 27663502; PubMed Central PMCID: PMCPMC5542030.
25. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet. 2014;46(11):1173-86. Epub 2014/10/06. doi: 10.1038/ng.3097. PubMed PMID: 25282103; PubMed Central PMCID: PMCPmc4250049.
26. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197-206. Epub 2015/02/13. doi: 10.1038/nature14177. PubMed PMID: 25673413; PubMed Central PMCID: PMCPmc4382211.
27. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45(11):1274-83. Epub 2013/10/08. doi: 10.1038/ng.2797. PubMed PMID: 24097068; PubMed Central PMCID: PMCPMC3838666.
28. Mehta NN. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Circ Cardiovasc Genet. 2011;4(3):327-9. Epub 2011/06/16. doi: 10.1161/circgenetics.111.960443. PubMed PMID: 21673312; PubMed Central PMCID: PMCPMC3125595.
29. Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, et al. Association analysis identifies 65 new breast cancer risk loci. Nature. 2017;551(7678):92-4. Epub 2017/10/24. doi: 10.1038/nature24284. PubMed PMID: 29059683; PubMed Central PMCID: PMCPMC5798588.
30. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47(9):979-86. Epub 2015/07/21. doi: 10.1038/ng.3359. PubMed PMID: 26192919; PubMed Central PMCID: PMCPMC4881818.
31. Scott RA, Scott LJ, Mägi R, Marullo L, Gaulton KJ, Kaakinen M, et al. An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. Diabetes. 2017;66(11):2888-902. Epub 2017/06/02. doi: 10.2337/db16-1253. PubMed PMID: 28566273; PubMed Central PMCID: PMCPMC5652602.
32. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell. 2018;173(7):1705-15.e16. Epub 2018/06/16. doi: 10.1016/j.cell.2018.05.046. PubMed PMID: 29906448; PubMed Central PMCID: PMCPMC6432650.
33. Chun S, Imakaev M, Hui D, Patsopoulos NA, Neale BM, Kathiresan S, et al. Non-parametric Polygenic Risk Prediction via Partitioned GWAS Summary Statistics. The American Journal of Human Genetics. 2020;107(1):46-59. doi: https://doi.org/10.1016/j.ajhg.2020.05.004.
34. So HC, Sham PC. Improving polygenic risk prediction from summary statistics by an empirical Bayes approach. Scientific reports. 2017;7:41262. Epub 2017/02/02. doi: 10.1038/srep41262. PubMed PMID: 28145530; PubMed Central PMCID: PMCPmc5286518.

35. Mak TSH, Porsch RM, Choi SW, Zhou X, Sham PC. Polygenic scores via penalized regression on summary statistics. Genet Epidemiol. 2017;41(6):469-80. Epub 2017/05/10. doi: 10.1002/gepi.22050. PubMed PMID: 28480976.
36. Nagpal S, Meng X, Epstein MP, Tsoi LC, Patrick M, Gibson G, et al. TIGAR: An Improved Bayesian Tool for Transcriptomic Data Imputation Enhances Gene Mapping of Complex Traits. The American Journal of Human Genetics. 2019;105(2):258-66. doi: https://doi.org/10.1016/j.ajhg.2019.05.018.
37. Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease from genome-wide association studies. American journal of human genetics. 2011;88(3):294-305. Epub 2011/03/08. doi: 10.1016/j.ajhg.2011.02.002. PubMed PMID: 21376301; PubMed Central PMCID: PMCPmc3059431.
38. Chatterjee N, Wheeler B, Sampson J, Hartge P, Chanock SJ, Park JH. Projecting the performance of risk prediction based on polygenic analyses of genome-wide association studies. Nat Genet. 2013;45(4):400-5, 5e1-3. Epub 2013/03/05. doi: 10.1038/ng.2579. PubMed PMID: 23455638; PubMed Central PMCID: PMCPmc3729116.
39. Hu Y, Lu Q, Powles R, Yao X, Yang C, Fang F, et al. Leveraging functional annotations in genetic risk prediction for human complex diseases. PLoS computational biology. 2017;13(6):e1005589. doi: 10.1371/journal.pcbi.1005589.
40. Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, Feldman M, et al. Analysis of polygenic risk score usage and performance in diverse human populations. Nature communications. 2019;10(1):3328. doi: 10.1038/s41467-019-11112-0.