A Comparison of Ten Polygenic Score Methods for Psychiatric Disorders Applied Across Multiple Cohorts

Supplement 1

See Supplement 2 (Excel document) for Supplementary Tables

Data

Schizophrenia GWAS summary statistics, were available from a total of 37 European ancestry cohorts reported in Pardiñas et al(1), comprising a total of 31K SCZ cases and 41K controls and 8M imputed SNPs. This included 34 cohorts from the PGC Schizophrenia (SCZ) Working group for which individual level genotype data were available. Detailed information about the cohorts is provided elsewhere(2) but is summarised in **Table S1**. PGS were calculated in each of the 30 PGC cohorts (target samples) using the GWAS discovery sample based on a meta-analysis of 37-2 = 35 cohorts i.e., the target sample was excluded from the discovery sample as well as a sample selected to be a tuning sample. Analyses were repeated using four different tuning samples, two of which were large (swe6:1094 cases and 1219 controls, gras: 1086 cases and 1232 controls) and two were small (lie2: 137 cases, 269 controls; msaf: 327 cases, 139 controls).

Major depression GWAS summary statistics from European ancestry studies comprised almost 13M imputed SNPs from 248K cases and 563K controls (3), which included data from the PGC Major Depressive Disorder (MDD) Working group (previously denoted as PGC29, but here MDD29). MDD29 includes data from 29 research study cohorts, described elsewhere (3-10) and summarised in **Table S2**. Individual level genotype data were available for 15K cases and 24K controls from 26 cohorts. We left one cohort out of those 26 cohorts in turn as the target sample, and then meta-analysed the remaining 28 samples with the other MDD GWAS summary statistics results to make the discovery samples. A cohort from Münster (3), not included in the discovery GWAS was used as the tuning sample (845 clinical defined MDD cases and 834 controls). Although the discovery sample meta-analyses include samples where the depression phenotype is self-reported rather than following a

structured clinical interview, we refer to the prediction as MDD since the PGC target cohorts are of MDD cases and controls.

The datasets stored in the PGC central server follow strict guidelines with local ethics committee approval.

Prediction methods

P-value based clumping and thresholding (PC+T)

In the PC+T method (also known as P+T or C+T)(11, 12) GWAS summary statistics are clumped to be approximately independent using a LD threshold, r^2. From this quasi-independent genome-wide SNP list, SNPs are selected by thresholding on a pre-specified association p-value, P_t. We evaluated PC+T as implemented in Ricopili (13) as used in analyses of the (Psychiatric Genomics Consortia) which uses PLINK (14) to clump the SNP set using $r^2 = 0.1$ within 500 kb windows, and $P_t \in$ (5e-08, 1e-06, 1e-04, 1e-03, 0.01, 0.05, 0.1, 0.2, 0.5, 1), where $P_t = 1$ means that all SNPs from the LD-clumped list are included. In applications of PC+T it is common for results from the most associated P_t to be reported (including the application in the software PRSice (15) which uses a continuous P_t range), but this approach utilises information from the target cohort and hence introduces a form of winner's curse. Here, the P_t threshold applied in target cohorts is the P_t threshold that maximised prediction in the tuning cohort.

SBLUP

SBLUP (16) is a method that re-scales the GWAS SNP effect estimates using an external LD reference panel to transform the ordinary least-squares estimates to approximate the best linear unbiased prediction (BLUP) solutions. This method assumes an infinitesimal model

where SNP effects are drawn from a normal distribution. All genome-wide SNPs are used to build the PGS. Hence, for example, consider a genomic region with a single causal variant but with many SNPs in the region correlated with the causal variant and correlated with each other. In this case the SBLUP effect size estimate is "smeared" across the correlated SNPs, but with the total contribution to risk expected to represent the best estimate of the signal from the underlying causal variant. This method is implemented within the software package GCTA (17).

LDpred2 and LDpred2-Inf

LDpred2 (18) uses the GWAS summary statistics and LD information from the external LD reference sample to infer the posterior mean effect size of each SNP, conditioning on the SNP effect estimates of other correlated SNPs. This method assumes a point-normal prior on the distribution of SNP effects such that only a fraction of SNPs with non-zero estimated effects are selected for inclusion in the PGS. LDpred2 has three hyperparameters: the fractions of causal SNPs (π, but denoted p in the original paper), SNP-based heritability (h_g^2), and sparsity. We used the same parameter setting as in (18). The fractions of causal SNPs π values are equally spaced on log scale, i.e. $\pi \in$ (0.00010, 0.00018, 0.00032, 0.00056, 0.00100, 0.00180, 0.00320, 0.00560, 0.01, 0.018, 0.032, 0.056, 0.1,0.18, 0.32, 0.56 ,1). The values for h_g^2 are set at 0.70, 1 and 1.40 folds of the LDSC estimate. The sparsity choices are "true" or "false". Normally, due to sampling variation, the SNPs in the subset with zero variance do not have exactly zero effect size; when sparsity is "true", it forces those SNPs with exactly zero effects. The hyperparameters that maximise the prediction in the tuning sample are applied in the target sample; those values can differ between target cohorts even though the same tuning cohort is used, reflecting the properties of the discovery sample which may change with each left-out target sample. LDpred2-Inf is equivalent to SBLUP as

the genetic architecture model assumes all SNPs have non-zero contribution of the phenotype variance. In software applications the results can differ because of the LD reference sample used and the assumptions for determining the LD window. The LD reference used in LDpred2 was the one provided on its website, which was calculated based on 362,320 UK Biobank individuals. Despite, the potential differences in the software applications, we observed a high concordance of results between SBLUP and LDPred-Inf (**Table S7**). LDpred2 applied here used the grid-model. We did not include the auto-model (which does not need a tuning sample), because firstly, the LDPred2 paper (18) shows it has similar performance to the grid-model. Secondly, the LDPred2 software requires individual level genotype data of the LD reference to implement the auto-model which is not provided with the software whereas it does provide an LD matrix derived from individual level genotype data. The LDpred2 was run genome-wide, instead of per chromosome, since it attains higher prediction accuracy(18).

LDpred-funct

LDpred-funct (19) is an extension of the LDpred-Inf (SBLUP equivalent) model but leverages trait-specific functional enrichments relative to the baseline-LD model (20) to up/down-weight SNP effects. The functional annotations include coding, conserved, regulatory and LD-related annotation. In the baseline-LD model, the enrichment of each category is jointly calculated via stratified LD score regression (21). LDpred-funct has a non-infinitesimal model version, but besides the discovery and training samples, it needs the phenotype of the target samples to identify a parameter (the number of bins, *K*, in the original paper (22)). Given that this method is still under peer review and given that we wish to avoid parameter estimation in the target sample, we continued only with the infinitesimal model version.

MegaPRS

We applied the MegaPRS (23) software based on the BLD-LDAK model as recommended by the authors. The BLD-LDAK model assumes the expected per SNP heritability varies with its MAF, LD, and functional annotation, compared to other compared methods (e.g. SBLUP, LDpred-Inf) that assume the expected per SNP heritability is constant (24). Based on the estimated per SNP heritability, MegaPRS constructs PGS using four priors: Lasso, Ridge, BOLT-LMM, BayesR. Each of those priors has different hyperparameters. We used the same parameters as the original paper (23), which generates 100 Lasso models, 11 Ridge regression, 132 BOLT-LMM, and 84 BayesR models. For BayesR the genetic architecture parameters are the same as SBayesR, assuming 4 distributions of SNP effects, but determining the π_i proportions and their scaling factors through a grid search in the tuning cohort. See the MegaPRS paper for more details of these methods, Zhang *et al*.(23). Following Zhang *et al*., we used 20K individuals with European ancestry from UK Biobank as the reference panel. The SNP annotation information used in the BLD-LDAK model were from ldak website (http://dougspeed.com/bldldak/).

Lassosum

Using GWAS summary statistics and a LD reference panel, Lassosum (25) constructs the PGS in a penalized regression framework. Lassosum is a deterministic method, and a convex optimization problem. It rescales the SNPs effect $\boldsymbol{\beta}$ by minimizing $f(\boldsymbol{\beta}) = \mathbf{y}^{\mathrm{T}}\mathbf{y} + (1-s)\boldsymbol{\beta}^{\mathrm{T}}\mathbf{X}_{\mathrm{r}}^{\mathrm{T}}\mathbf{X}_{\mathbf{r}}\boldsymbol{\beta} - 2\boldsymbol{\beta}^{\mathrm{T}}\mathbf{X}^{\mathrm{T}}\mathbf{y}$+s$\boldsymbol{\beta}^{\mathrm{T}}\boldsymbol{\beta}$+2 $\lambda\|\boldsymbol{\beta}\|_1^1$, where $\mathbf{y}$ is the vector of phenotypes, $\mathbf{X}_{\mathrm{r}}$ is the genotype of LD reference; $\mathbf{X}$ is the genotype data of discovery sample, but this is not needed because $\mathbf{X}^{\mathrm{T}}\mathbf{y}/\mathrm{N}$ is the GWAS summary statistics that is known. Same as the original method paper, s set as 0.2, 0.5, 0.9, or 1. λ are 20 values sequenced between 0.001 and 0.1 that

equally spaced on the log-scale. The optimal hyperparameters for s and λ are identified in the tuning cohort. The current version of Lassosum cannot take a reference panel larger than 20K, and 5K is suggested (https://github.com/tshmak/lassosum). Hence, 5K unrelated UK Biobank individuals were randomly selected as the reference panel. We used only HapMap3 SNPs.

PRS-CS and PRS-CS-auto

PRS-CS (26) is also built under a Bayesian regression framework. Unlike LDpred2 which assumes a point-normal distribution as a prior, which is discrete, PRS-CS assumes a continuous shrinkage prior on the SNP effects. PRS-CS was implemented using the software default settings and with the LD reference panel provided with the PRS-CS software, which is computed using the 1000 Genomes samples and HapMap3 SNPs. In PRS-CS, for the global scaling parameter which is applied to all SNP effects ϕ, the search grid is $\phi^{1/2} \in$ (0.0001, 0.001, 0.01, 0.1, 1). The ϕ that produces the best predictive performance in a tuning data set is selected for use in the target sample. In PRS-CS-auto, ϕ is automatically learnt from GWAS summary statistics and no tunning sample is needed. ψ is a local marker-specific parameter which is drawn from the Gamma distribution, i.e. $\psi_j \sim Gamma(a, \delta_j)$ and $\delta_j \sim Gamma(b, 1)$. We used the default parameters proposed by the authors of a = 1 and b = 0.5.

SBayesR

SBayesR (27) is a method that re-scales the GWAS SNP effect estimates based on Bayesian multiple regression. SBayesR assumes that the standardised SNP effects are drawn from a mixture of C=4 zero-mean normal distributions with different variances (one of the variances is zero, with a probability of π_1), indicating that only a fraction of SNPs (1-π_1) have non-zero

estimated effects which contribute to the phenotype. Moreover, the contributions of SNPs in different distributions differ because of different variances. Here, we evaluated SBayesR in the default setting. The scaling factor γ for the variance of each mixture component are set as 0, 0.01, 0.1, and 1 in this order. The banded LD matrix was downloaded from GCTB website (https://cnsgenomics.com/software/gctb/#Download), which was built based on the HapMap3 SNPs of randomly selected and unrelated 10K UK Biobank individuals. The windows size used to estimate the LD is 3cM, which is the same as LDpred2. Whereas LDpred2 estimates π from a tuning sample, SBayesR estimates π from the GWAS discovery sample, so no tuning sample is needed. LDpred2 has an auto version which does need the tuning sample, but it requires individual level genotype data of the LD reference which is not provided with the software whereas it does provide an LD matrix derived from individual level genotype data.

AUC vs variance explained on the liability scale

Although covariates were not included when calculating AUC the impact is small. For example, for SCZ the maximum median variance in liability was for MegaPRS at 9.2%. Assuming lifetime risk of SCZ of 0.01 the AUC expected from normal distribution theory(4) (see pseudo-code section) is 0.722, compared to the mean reported of 0.731. For MDD the maximum median variance in liability was for SBayesR at 3.5%. Assuming a lifetime risk of 0.15 the expected AUC is 0.596 compared to the mean reported of 0.599. The AUC and variance in liability from the model including 6 principal components and PGS in the regression is in Table S3 and Table S5.

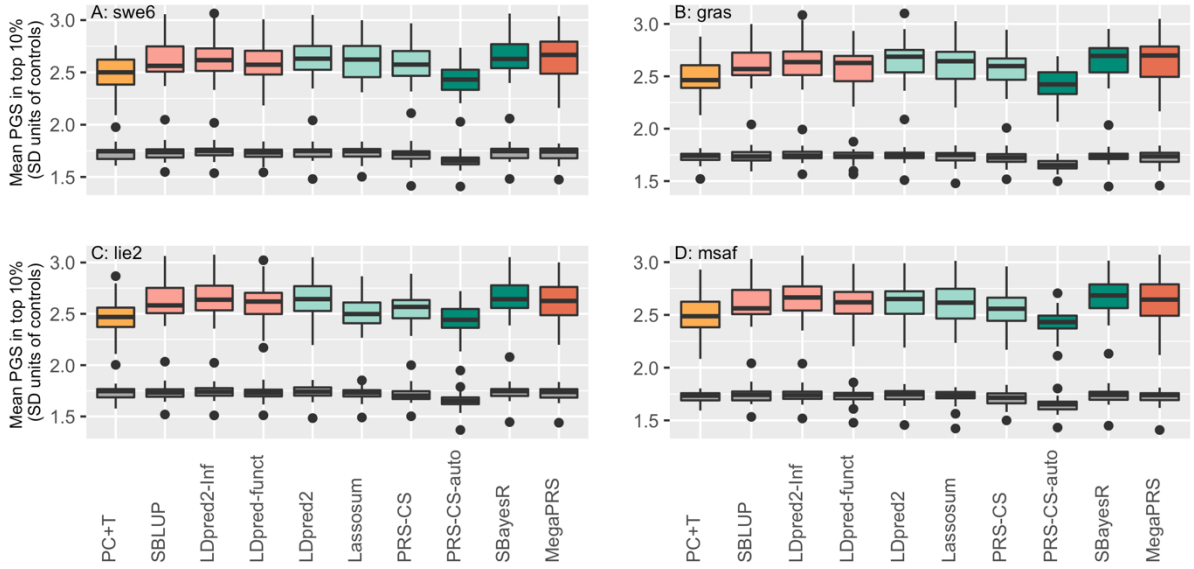


Figure S1. PGS in top 10% of SCZ cases and controls.

The mean of the PGS for the top 10% cases (colored boxes) and for the top 10% of controls (grey boxes) in PGS standard deviation (SD) unit scale. The controls have mean PGS of zero and SD of 1. Subfigures are the results using different tuning cohorts.

Since the PGS are normally distributed, as expected the mean PGS for controls in the top 10% PGS is ~1.75 SD units, whereas the top 10% of cases have mean value of 2.65 control sample SD units using SBayesR. These mean values of the top 10% in cases equate to expectations from the population of the top 1.1% SCZ.

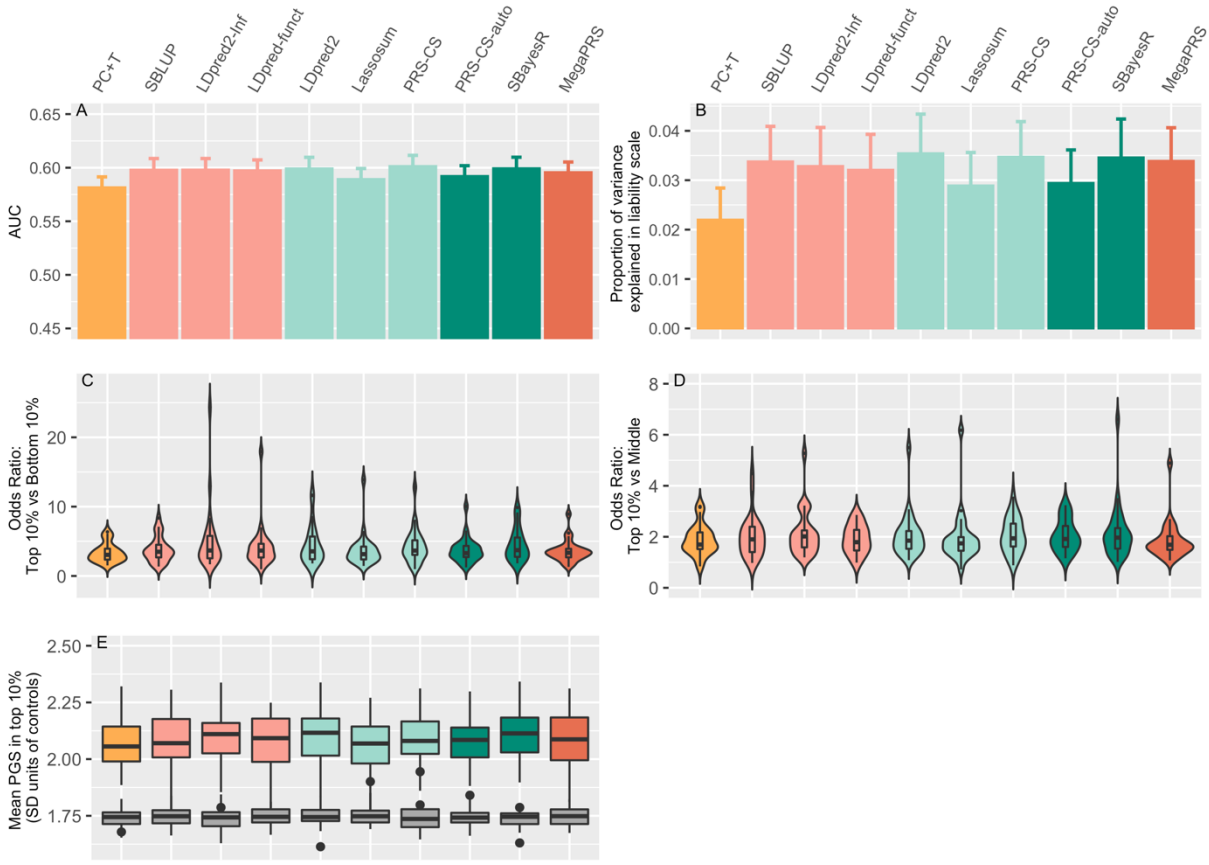


Figure S2. Prediction of MDD case/control status using different PGS methods.

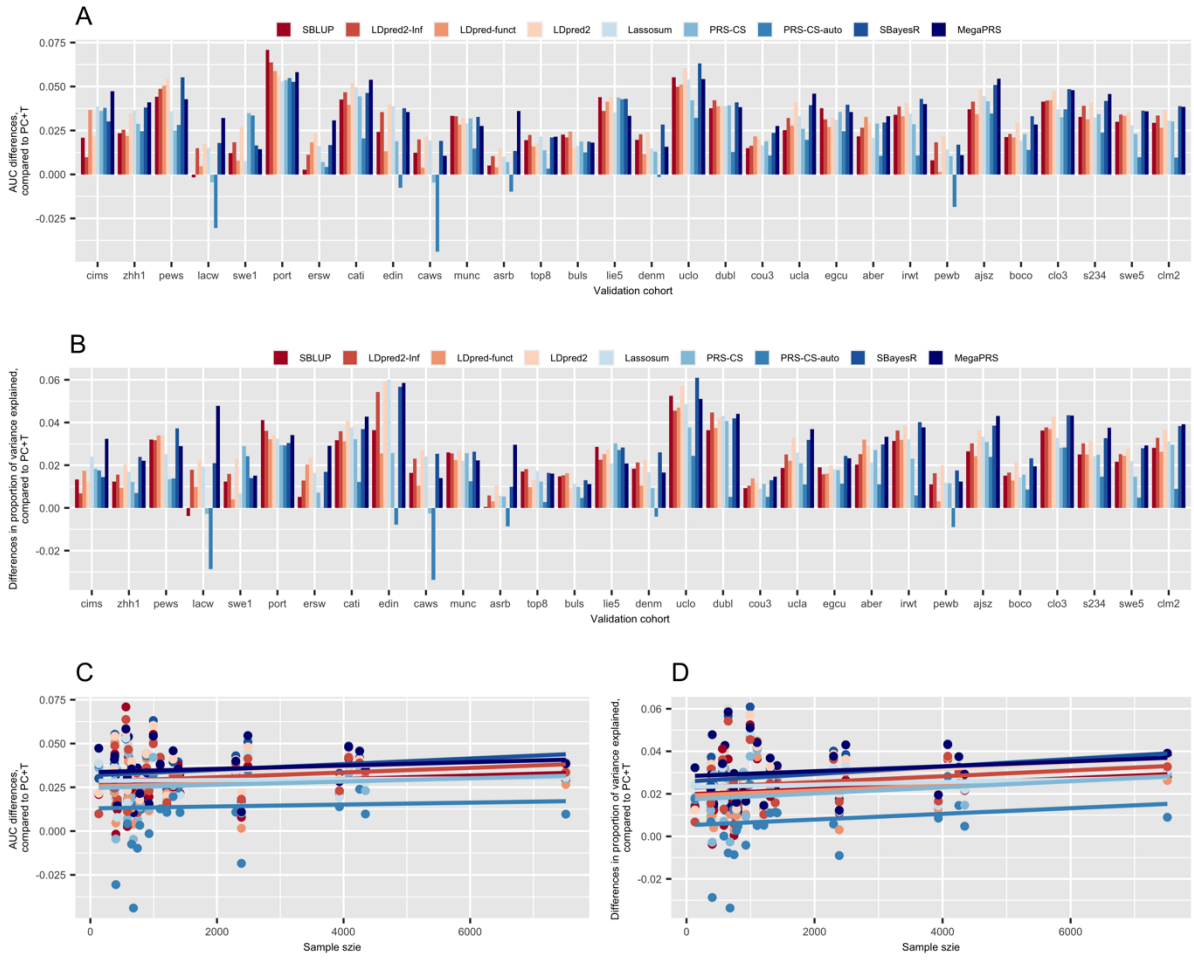
A) The area under curve (AUC) statistic. The AUC is a measure for the prediction accuracy, which indicates the probability that a case ranks higher than a control. The predictors were constructed from GWAS summary statistics of UK Biobank(4, 28), 23andMe(5), GERA(29), iPSYCH (7), deCODE (8), GenScotland (9, 10), PGC-MDD29 excluding the target cohort. The target cohorts comprised 26 of the 29 cohorts in MDD29. A cohort from Münster (845 clinical defined MDD cases and 834 controls), not included in the MDD29, was used as the tuning sample. Each bar reflects the median AUC across 26 target cohorts, the whiskers show the 95% confidence interval for comparing medians.

B) The proportion of variance explained by PGS on the scale of liability, assuming a population lifetime risk of 15%.

C) The odds ratio when considering the odds of being a case comparing the top 10% vs bottom 10% of PGS.

D) The odds ratio when considering the odds of being a case comparing the top 10% vs those in the middle of the PGS distribution, calculated as the averaged odds ratio of the top 10% ranked on PGS relative to the 5^{th} decile and 6^{th} decile.

E) The mean of the PGS for the top 10% cases (coloured boxes) and for the top 10% of controls (grey boxes) in PGS standard deviation (SD) unit scale so that controls have mean PGS of zero and SD of 1. Since the PGS are normally distributed, as expected the mean PGS for controls in the top 10% PGS is ~1.75 SD units, whereas the top 10% of cases have mean value of 2.10 control sample SD units for MDD cases, using SBayesR. These mean values of the top 10% in cases equate to expectations from the population of the top 4.7% for MDD.


A
SBLUP
LDpred2-Inf
LDpred-funct
LDpred2
Lassosum
PRS-CS
PRS-CS-auto
SBayesR
MegaPRS
AUC differences, compared to PC+T
0.075
0.050
0.025
0.000
-0.025
cims zhh1 pews lacw swe1 port ersw cati edin caws munc asrb top8 buls lie5 denm uclo dubl cou3 ucla egcu aber irwt pewb ajsz boco clo3 s234 swe5 clm2
Validation cohort
B
Differences in proportion of variance explained, compared to PC+T
0.06
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4000
6000

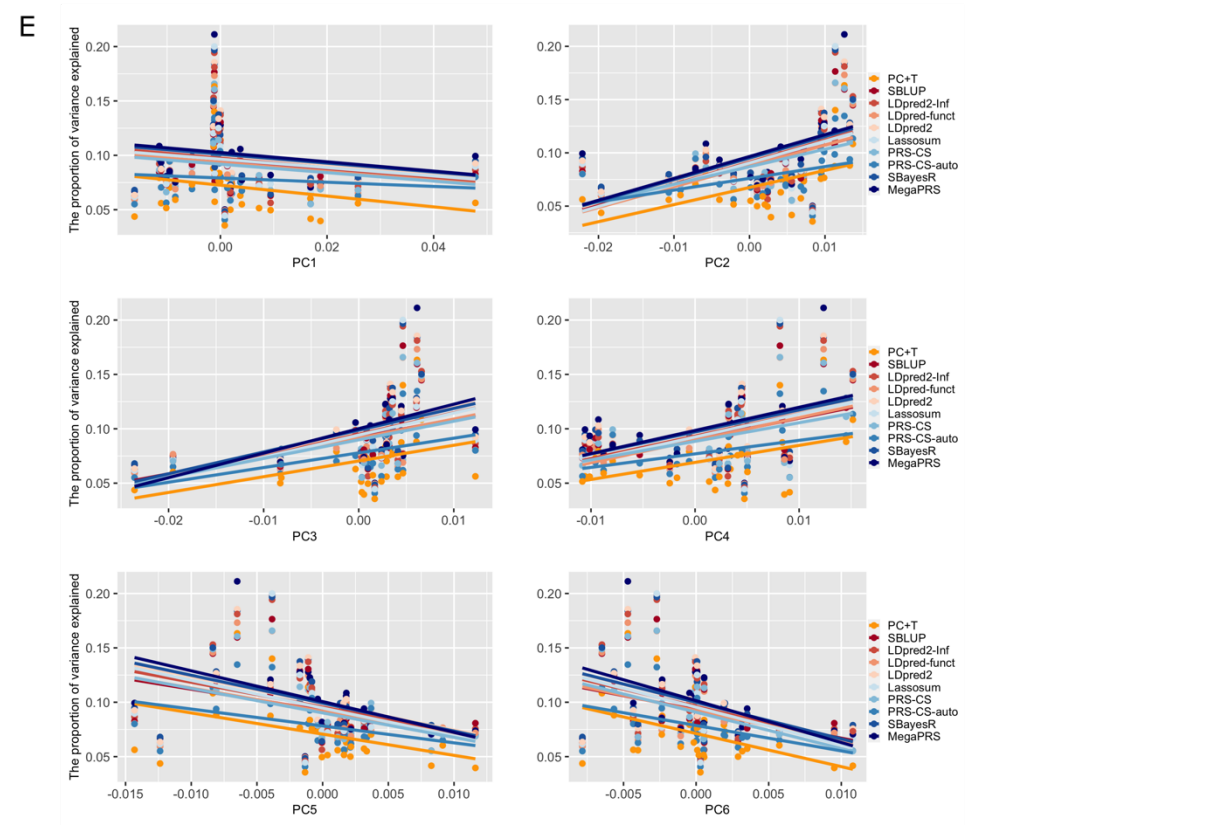
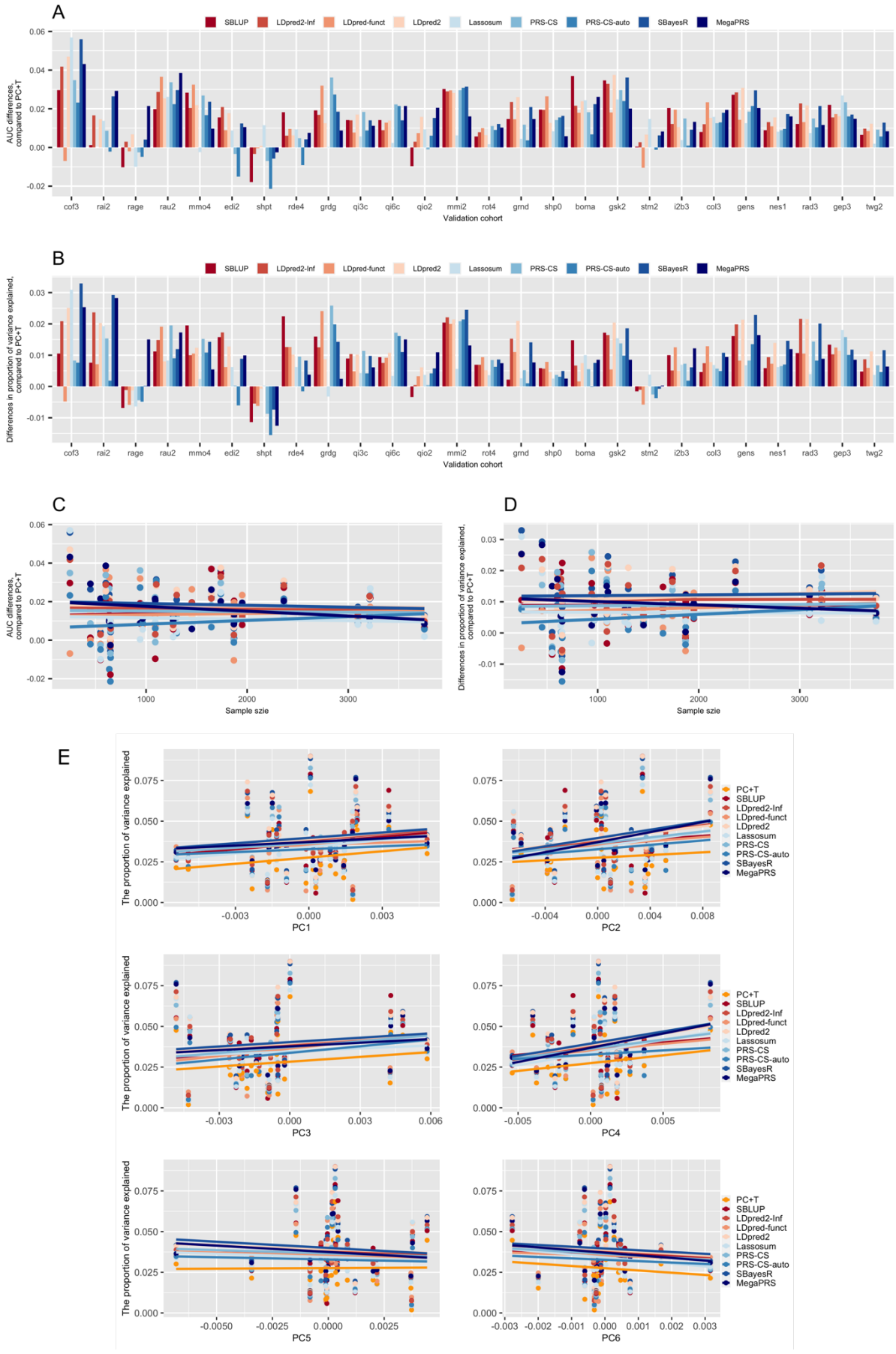

E
The proportion of variance explained
0.20
0.15
0.10
0.05
PC1
PC2
PC3
PC4
PC5
PC6
PC+T
SBLUP
LDpred2-Inf
LDpred-funct
LDpred2
Lassosum
PRS-CS
PRS-CS-auto
SBayesR
MegaPRS

Figure S3. Individual SCZ cohort results and relationship with potential confounders.

The area under the curve (A and C panels) and the proportion of variance explained by PGS on the liability scale (B and D panels) of schizophrenia predicted by different PGS methods in each of target cohorts, compared to PC+T method. x-axis of A and B are the target cohorts ordered by sample size, increasing from left (Ncases = 71, Ncontrols =69) to right (Ncases = 3466, Ncontrols =4297). x-axis of C and D are the sample sizes of each target cohorts. The lines in C and D are the regression lines of y and x by each method. For each method, when regressing AUC difference on the sample size of the target cohort, the p-values are all larger than 0.05. Similarly, the p-values of regressing the proportion of variance explained by PGS on the sample size are larger than 0.05. E) The proportion of variance explained on the liability scale against first 6 principal components (PCs), which were estimated from directly genotyped SNPs shared across cohorts. The x-axis is the mean value of the PC in the cohort. The regression p-values were: PC1: 0.25-0.56, PC2: 0.001-0.004, PC3: 0.014-0.052, PC4: 0.004-0.024, PC5: 0.016-0.049, PC6: 0.009-0.056, with the range reflecting different methods. Using the 23 European cohorts collected in a single country, we found in regression of each PC on latitude, longitude and SNP-array (Affymetrix, Illumina-nonOmni, Illumina Omi) the following significant associations (P<0.01): PC1: latitude & Array, PC2: longitude, PC3: latitude & longitude, PC4: Array, PC5: latitude & array, recognising that latitude and longitude could represent phenotype as well as genetic ancestry differences.


A
SBLUP
LDpred2-Inf
LDpred-funct
LDpred2
Lassosum
PRS-CS
PRS-CS-auto
SBayesR
MegaPRS
AUC differences, compared to PC+T
0.06
0.04
0.02
0.00
-0.02
cof3 rai2 rage rau2 mmo4 edi2 shpt rde4 grdg qi3c qi6c qio2 mmi2 rot4 grnd shp0 boma gsk2 stm2 i2b3 col3 gens nes1 rad3 gep3 twg2
Validation cohort
B
SBLUP
LDpred2-Inf
LDpred-funct
LDpred2
Lassosum
PRS-CS
PRS-CS-auto
SBayesR
MegaPRS
Differences in proportion of variance explained, compared to PC+T
0.03
0.02
0.01
0.00
-0.01
cof3 rai2 rage rau2 mmo4 edi2 shpt rde4 grdg qi3c qi6c qio2 mmi2 rot4 grnd shp0 boma gsk2 stm2 i2b3 col3 gens nes1 rad3 gep3 twg2
Validation cohort
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AUC differences, compared to PC+T
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0.04
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Differences in proportion of variance explained, compared to PC+T
0.03
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0.01
0.00
-0.01
1000
2000
3000
Sample szie
E
The proportion of variance explained
0.075
0.050
0.025
0.000
-0.003
0.000
0.003
PC1
-0.004
0.000
0.004
0.008
PC2
-0.003
0.000
0.003
0.006
PC3
-0.005
0.000
0.005
PC4
-0.0050
-0.0025
0.0000
0.0025
PC5
-0.003
-0.002
-0.001
0.000
0.001
0.002
0.003
PC6
PC+T
SBLUP
LDpred2-Inf
LDpred-funct
LDpred2
Lassosum
PRS-CS
PRS-CS-auto
SBayesR
MegaPRS

Figure S4. Individual MDD cohort results and relationship with potential confounders.

The area under the curve (A and C panels) and the proportion of variance explained by PGS on the liability scale (B and D panels) of major depression predicted by different PGS methods in each of target cohorts, compared to PC+T method. x-axis of A and B are the target cohorts ordered by sample size, increasing from left (Ncases = 120, Ncontrols =126) to right (Ncases = 1,097, Ncontrols =2,663). x-axis of C and D are the sample sizes of each target cohorts. The lines in C and D are the regression lines of y and x for each method. For each method, when regressing AUC difference on the sample size of the target cohort, the p-values are all larger than 0.05. Similarly, the P-values of regressing the proportion of variance explained by PGS on the sample size are larger than 0.05. E) The proportion of variance explained on the liability scale against first 6 principal components (PCs), which were estimated from directly genotyped SNPs shared across cohorts. The x-axis is the mean value of the PC in the cohort. The regression p-values were: PC1: 0.39-0.76, PC2: 0.09-0.65, PC3: 0.28-0.64, PC4: 0.16-0.68, PC5: 0.62-0.96, PC6: 0.59-0.85, with the range reflecting different methods. Using the 15 European cohorts collected in a single country, we found in regression of each PC on latitude, longitude and SNP-array (Affymetrix, Illumina-nonOmni, Illumina Omi) the following significant associations (P<0.01): PC1: latitude, PC2: longitude, recognising that latitude and longitude could represent phenotype as well as genetic ancestry differences.

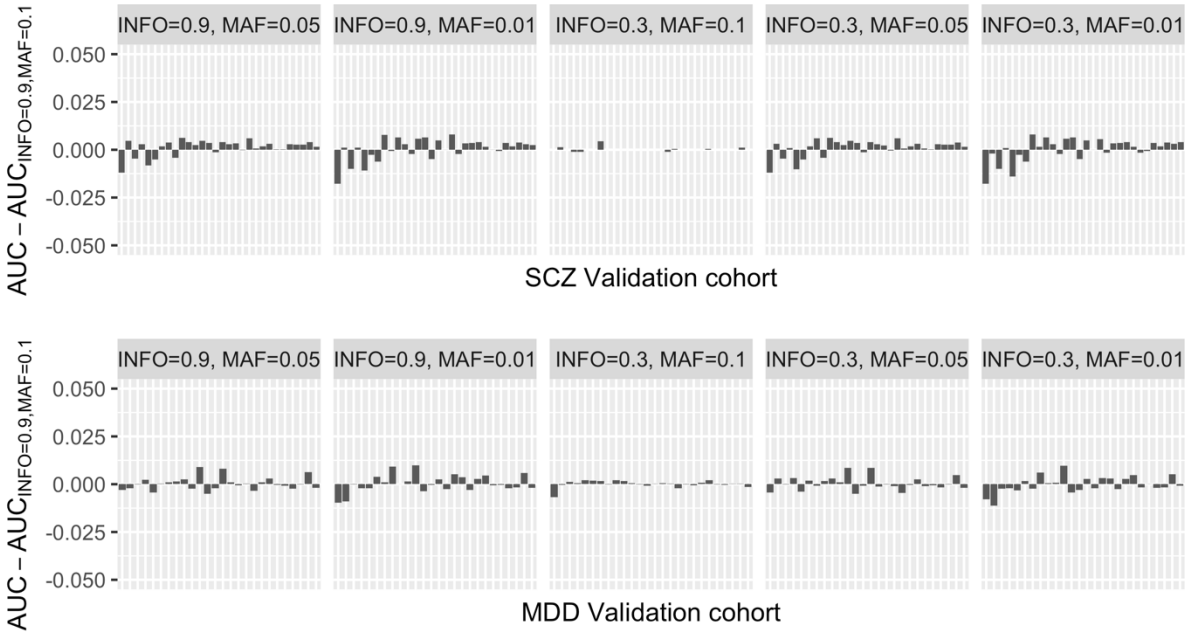

Figure S5. Sensitivity analysis: INFO score and MAF.

Differences in AUC of SBayesR when using different quality control thresholds.

The different bars refer to different target cohorts ordered by its sample size.

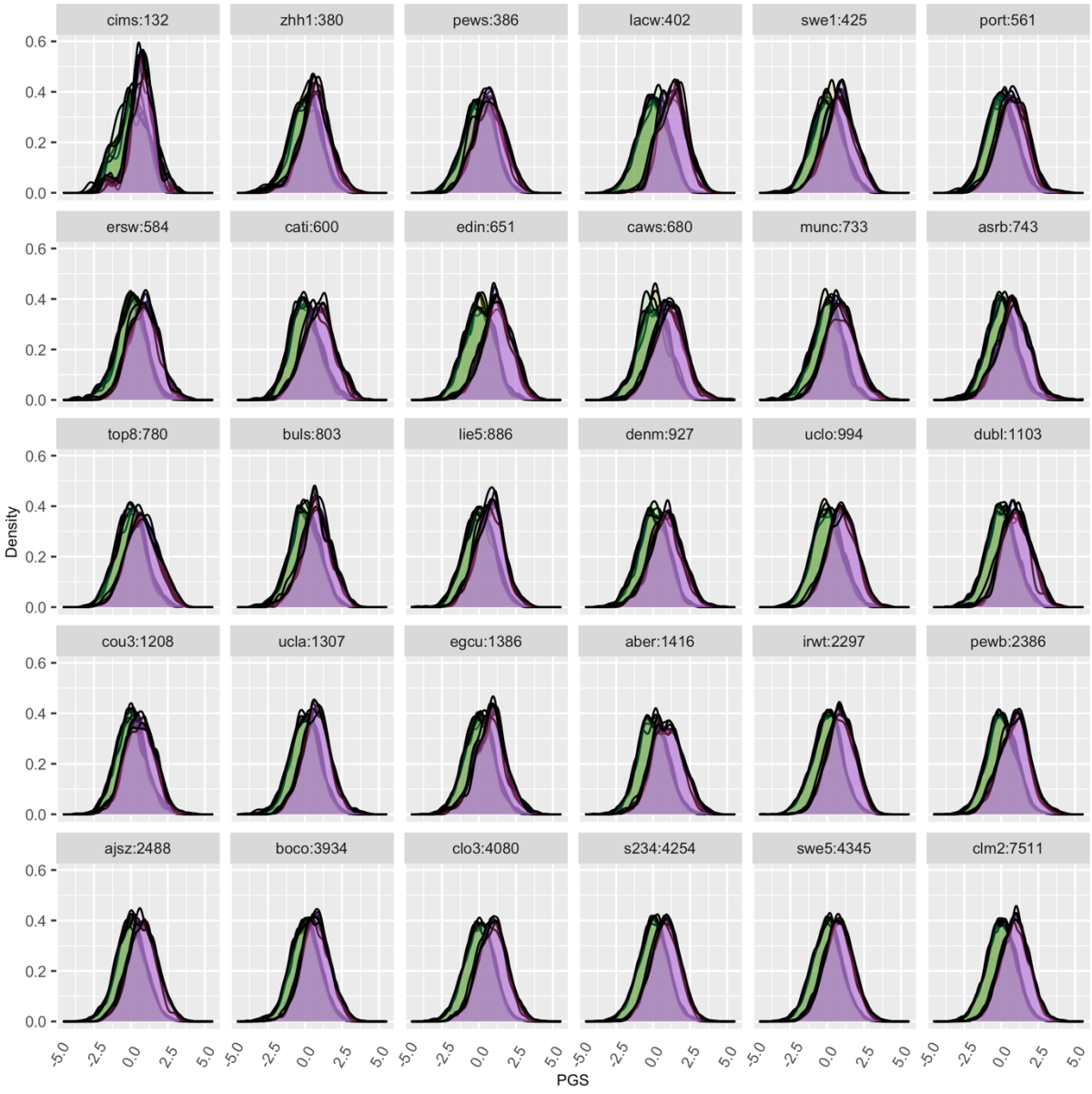

Figure S6. PGS densities of SCZ cases and controls in each target cohort ordered by sample size.

Light green shows the PGS density of controls predicted by different methods. Light purple shows the PGS density of cases predicted by different methods. The PGS were scaled to SD units of controls. Thus, the mean and variance of PGS in controls are zero and one, respectively. The mean and variance of PGS in cases are in Table S3 (SD of PGS of cases (SD units of controls)).

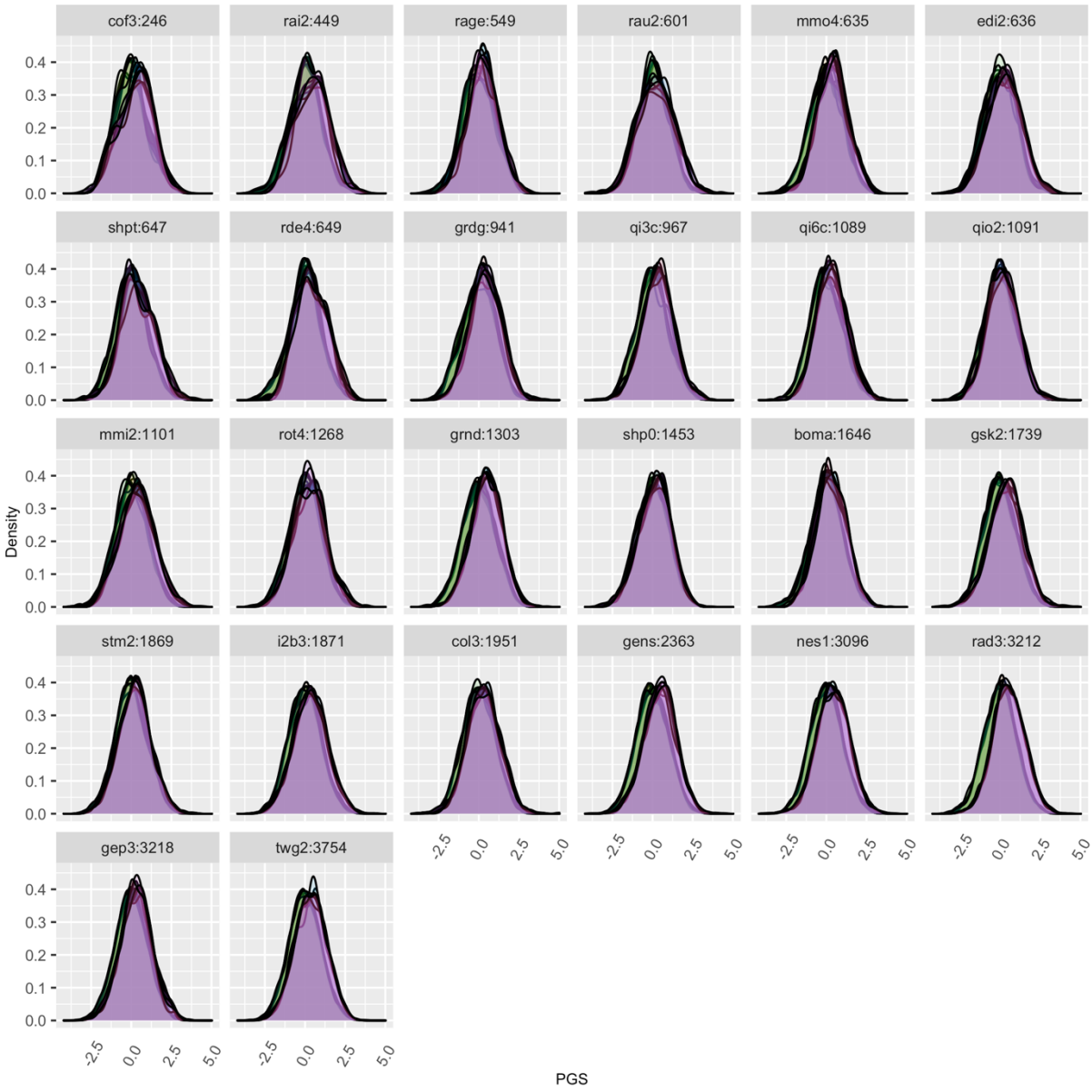

Figure S7. PGS densities of MDD cases and controls each target cohort ordered by sample size.

Light green shows the PGS density of controls predicted by different methods. Light purple shows the PGS density of cases predicted by different methods. The PGS were scaled to SD units of controls. Thus, the mean and variance of PGS in controls are zero and one, respectively. The mean and variance of PGS in cases are in Table S5 (SD of PGS of cases (SD units of controls)).

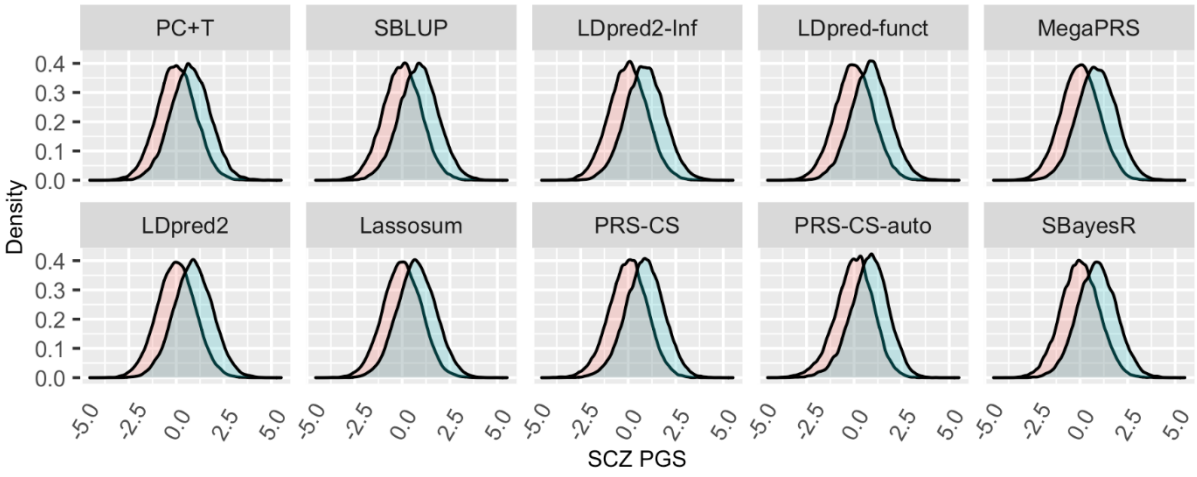

Figure S8. PGS densities of SCZ cases and controls estimated by different methods across the target cohorts.

The mean PGS of cases is, on average, 0.85 standard deviation units (calculated in controls) and refer to Table S3 for estimate of each method.

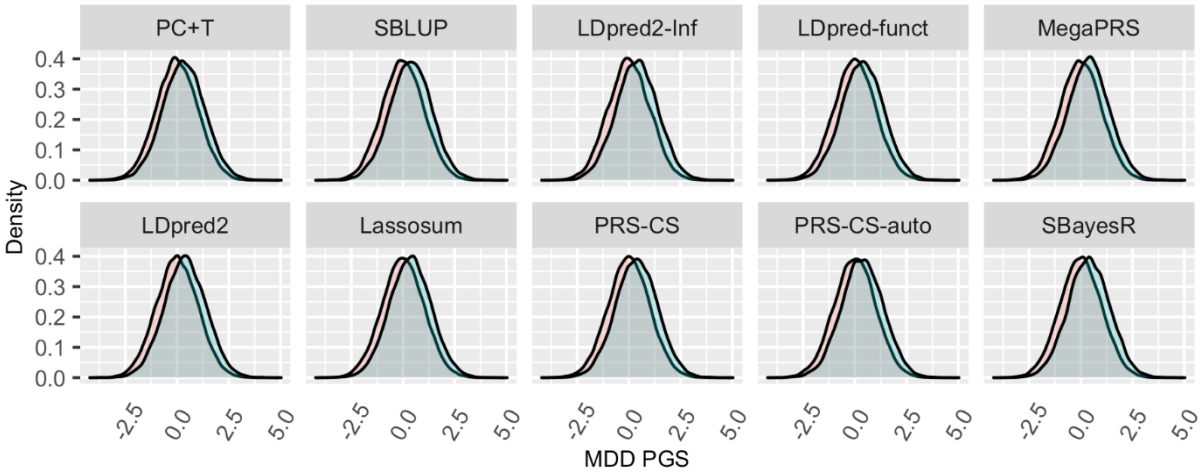

Figure S9. PGS densities of MDD cases and controls estimated by different methods across the target cohort.

The mean PGS of cases is, on average, 0.34 standard deviation units (calculated in controls) and refer to Table S5 for estimate of each method.

Pseudo code

```
#########################################################
# PC+T
#########################################################
clump_nav3 --noindel \
--pfile gwas_no_val_tun.gz \
--hq_f .01 \
--hq_i .6 \
--outname $coh_clumpOut \
 --clu_p1 1.0 \
--clu_p2 1.0 \
--clu_window 500 \
--clu_r2 0.1 \
--refdir 1KG/pop_EUR \
--popname eur


#########################################################
# SBLUP
#########################################################
gcta64 --bfile LD_reference \
--chr chrid \
--cojo-file daner_no_gwas.ma \
--cojo-sblup lambda \
--cojo-wind 1000 \
--thread-num 5 \
--out scz_tun_chr_sblup_prs


#########################################################
# LDpred2  Inf+grid
#########################################################
info_snp <- snp_match(sumstats, map_ldref)
sd_ldref <- with(info_snp, sqrt(2 * af_UKBB * (1 - af_UKBB)))
sd_ss <- with(info_snp, 2 / sqrt(n_eff * beta_se^2))

is_bad <-
  sd_ss < (0.5 * sd_ldref) | sd_ss > (sd_ldref + 0.1) | sd_ss < 0.1 | sd_ldref < 0.05

df_beta <- info_snp[!is_bad, ]

tmp <- tempfile(tmpdir = "tmp-data")

for (chr in 1:22) {
  cat(chr, ".. ", sep = "")
  ind.chr <- which(df_beta$chr == chr)
  ind.chr2 <- df_beta$`_NUM_ID_`[ind.chr]
  ind.chr3 <- match(ind.chr2, which(map_ldref$chr == chr))
  corr_chr <- readRDS(paste0("ld-ref/LD_chr", chr, ".rds"))[ind.chr3, ind.chr3]
```

```
  if (chr == 1) {
    corr <- as_SFBM(corr_chr, tmp)
  } else {
    corr$add_columns(corr_chr, nrow(corr))
  }
}

# Heritability estimation of LD score regression
(ldsc <- with(df_beta, snp_ldsc(ld, ld_size = nrow(map_ldref),
                                chi2 = (beta / beta_se)^2,
                                sample_size = n_eff,
                                ncores = NCORES)))
h2_est <- ldsc[["h2"]]

# LDpred2-inf
beta_inf <- snp_ldpred2_inf(corr, df_beta, h2 = h2_est) ##beta output
beta_inf_out<-cbind(df_beta[,c('rsid','a0','a1')],beta_inf)
print("finished beta_inf")

#LDpred2-grid
(h2_seq <- round(h2_est * c(0.7, 1, 1.4), 4))
(p_seq <- signif(seq_log(1e-4, 1, length.out = 17), 2))

params <- expand.grid(p = p_seq, h2 = h2_seq, sparse = c(FALSE, TRUE))
beta_grid <- snp_ldpred2_grid(corr, df_beta, params, ncores = NCORES)
beta_grid<-as.data.frame(beta_grid)
colnames(beta_grid)<-paste(params$p,params$h2,params$sparse,sep='_')

betaall<-cbind(beta_inf_out,beta_grid)

write.table(betaall,file='ldpred2.scores',col.names=T,row.names=F
            ,append=F,quote=F,sep='\t')
print("finished beta_grid")


#########################################################
# ldpredfunct
#########################################################
Python-2.7.9/python ldpredfunct.py \
--gf=LD_reference \
--FUNCT_FILE=functional_matrix_no_val.txt \
--coord=coord_out_no_val_tun \
--ssf=gwas \
--N=N \
--H2=h2 \
--out=no_tun_tun_ldpredfunct_prs \
--posterior_means=no_coh_tun_ldpredfunt_out

#########################################################
# lassosum
```

```
#####################################################
library(lassosum)
library(parallel)
library(data.table)

ss<-fread(trainGWAS,header=TRUE)
cor<-p2cor(p=ss$P,n=ss$NMISS,sign=log(ss$OR),min.n=3000)
ref.bfile<-'ukbEURu_hm3_all_v3_5k'
cl <- makeCluster(5)
out<-lassosum.pipeline(cor=cor,chr=ss$CHR,pos=ss$BP
                       ,A1=ss$A1,A2=ss$A2
                       ,ref.bfile=ref.bfile
                       ,LDblocks='EUR.hg19'
                       ,trace=1
                       ,destandardize=F
                       ,cluster=cl)
betalist<-out$beta
#one<-betalist$0.2
betaout<-as.data.frame(matrix(unlist(betalist),byrow=F,ncol=80))
colnames(betaout)<-paste(rep(paste0('S ',names(betalist)),each=20),1:20,sep='_')
betaout<-cbind(out$sumstats,betaout)


#####################################################
# PRS-CS
#####################################################
for chrid in {1..22}
do
for pv in 1e-06 1e-05 1e-04 1e-03 1e-02 1e-01 1e+00
do

/Python-2.7.9/python PRScs.py --ref_dir=LD_reference \
--bim_prefix=gwas.bim \
--sst_file=daner_no_val_tun.prscs \
--n_gwas=sample_size \
--out_dir=val_tun_chr \
--chrom=${chrid} \
--phi=${pv}
done
done

#####################################################
# PRS-CS-auto
#####################################################
for chrid in {1..22}
do
/Python-2.7.9/python /PRScs.py --ref_dir=LD_reference \
--bim_prefix=gwas.bim \
--sst_file=daner_no_val_tun.prscs \
--n_gwas=sample_size \
```

```
--out_dir=val_tun_chr \
--chrom=${chrid}
done

#####################################################
# SBayesR
#####################################################
gctb --sbayes R \
--mldm /ukbEURu_hm3_mldm_list.txt \
--pi 0.95,0.02,0.02,0.01 \
--gamma 0.0,0.01,0.1,1 \
--gwas-summary /daner_no_gwas.ma \
--chain-length 10000 \
--burn-in 2000 \
--exclude-mhc \
--out-freq 10 \
--out daner_no_gwas_sbayesr


#####################################################
# MegaPRS
#####################################################
#Use SumHer to estimate total and per-SNP heritability given BLD-LADK model
ldak5.1.linux.fast --cut-weights sections --bfile UKB_LD50k
ldak5.1.linux.fast --calc-weights-all sections --bfile UKB_LD50k
mv sections/weights.short bld65
#[NOTE bld1…bld64 were download from LDAK Website]

ldak5.1.linux.fast --calc-tagging bld.ldak --bfile UKB_LD50k --ignore-weights YES \
   --power -.25 --annotation-number 65 --annotation-prefix bld --window-kb 1000 --save-
matrix YES

# identify high LD region
ldak5.1.linux.fast --cut-genes highld --bfile UKB_LD50k --genefile highLD.txt

# Run SumHer
ldak5.1.linux.fast --sum-hers train_tun_val_bld --tagfile bld.ldak.tagging \
   --summary size_train_tun_val.ldak --check-sums NO --matrix bld.ldak.matrix \
   --exclude genes.predictors.used

#  Prediction
# Step 1 - Calculate predictor-predictor correlations
ldak5.1.linux.fast  --bfile UKB_LD50k --calc-cors ukb_cors --window-kb 3000

# Step 2- Estimate effect sizes for training and full prediction models
ldak5.1.linux.fast \
     --mega-prs tun_val_bld \
     --model mega \
     --bfile UKB_LD50k  \
     --cors ukb_cors \
```

```
    --ind-hers train_tun_val_bld.ind.hers \
    --summary size_loo_tun_val.ldak # [note: training + testing cohorts (full GWAS)]
    --summary2 size_train_tun_val.ldak # [note: training cohort only]
    --window-kb 1000 --allow-ambiguous YES \
    --extract comm_tunval_2

# Step 3 - Determine the best model
ldak5.1.linux.fast --calc-scores tun_val_bld \
    --bfile UKB_LD50k \
    --scorefile tun_val_bld.effects.train \
    --summary tun.ldak # [Note GWAS of testing cohort]
    --power 0 \
    --final-effects tun_val_bld.effects.final \
    --extract commsnp_tunval_3 # [note use only overlapped SNPs]
    --allow-ambiguous YES \
    --exclude genes.predictors.used

#######################################################
#subroutine to calculate from normal distribution theory the
# Wray NR, Yang J, Goddard ME, Visscher PM (2010) The Genetic Interpretation of Area
#               under the ROC Curve in Genomic Profiling.
# PLoS Genet 6(2): e1000864. doi:10.1371/journal.pgen.1000864
r2toAUC<-function(K,r2){
  # K = Probability of disease (lifetime risk of disease)
  # r2 = variance explained by PRS (or any predictor)
  T0 = qnorm(1-K) #threshold for K
  z = dnorm(T0)   #height of normal distrubution at threshold
  i = z/K        # mean liability of case (Phneotypic SD=1)
  v = -i*K/(1-K) #mean liability of controls
  k =  i*(i-T0)  #variance reduction factor of cases
  kv = v*(v-T0)  #variance reduction factor of contro
  vcase=r2*(1-r2*k) # variance in PRS in cases
  vcont=r2*(1-r2*kv)  # variance in PRS in controls
#probaility a case ranks higher than a control
  auc=pnorm((i-v)*r2/(sqrt(vcase+vcont)))

  return(list(auc=auc))
}

#######################################################
Pseudo code for AUC
#######################################################

AUC:
library(pROC)
tstS = glm(Pheno01~PGS, data, family = binomial(logit)) # logit model
aucvS = auc(data$ Pheno01,tstF$linear.predictors)


AUC*:
```

```
 tstF = glm(Pheno01~PGS+6PCs, data, family = binomial(logit)) # logit model
 aucvF = auc(data$ Pheno01,tstF$linear.predictors)


#########################################################
Pseudo code for variance explained in liability scale
#########################################################
# Lee et al (2012) A Better Coefficient of Determination for Genetic Profile Analysis.
# Genetic Epidemiology 36 : 214–224
# DOI: 10.1002/gepi.21614
Variance explained in liability scale:
lm0=lm(std_y~1,data)
lmr=lm(std_y~6PCs, data)
lmf=lm(std_y~PGS+6PCs, data)

R2v=1-exp((2/N)*(logLik(lmr)-logLik(lmf)))
R2=1-exp((2/N)*(logLik(lm0)-logLik(lmf)))

h2l_r2 = h2l_R2(K,R2v,P) # Variance explained in liability scale
h2l_r2_cov = h2l_R2(K,R2,P) #In our Supplementary Tables this is noted with *)


h2l_R2 <- function(k, r2, p) {
  # K baseline disease risk
  # r2 from a linear regression model attributable to genomic profile risk score
  # P proportion of sample that are cases
  # calculates proportion of variance explained on the liability scale
  x= qnorm(1-k)
  z= dnorm(x)
  i=z/k
  C= k*(1-k)*k*(1-k)/(z^2*p*(1-p))
  theta= i*((p-k)/(1-k))*(i*((p-k)/(1-k))-x)
  h2l_R2 = C*r2 / (1 + C*theta*r2)
}
```

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