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Supplemental Data

Joint Analysis of Psychiatric Disorders Increases Accuracy of Risk Prediction for Schizophrenia, Bipolar Disorder, and Major Depressive Disorder

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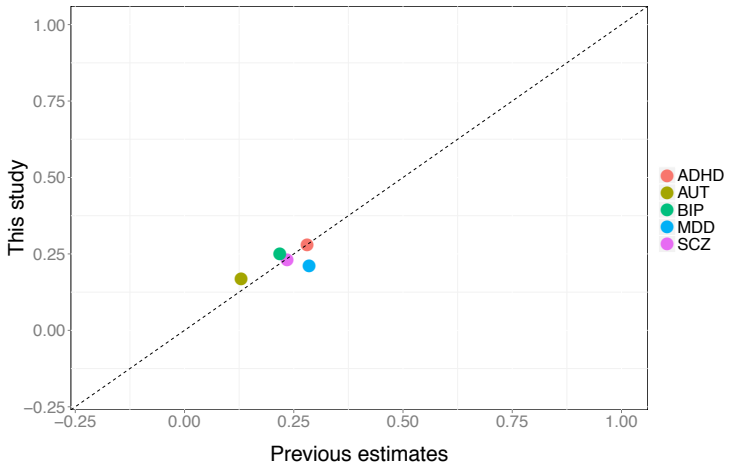
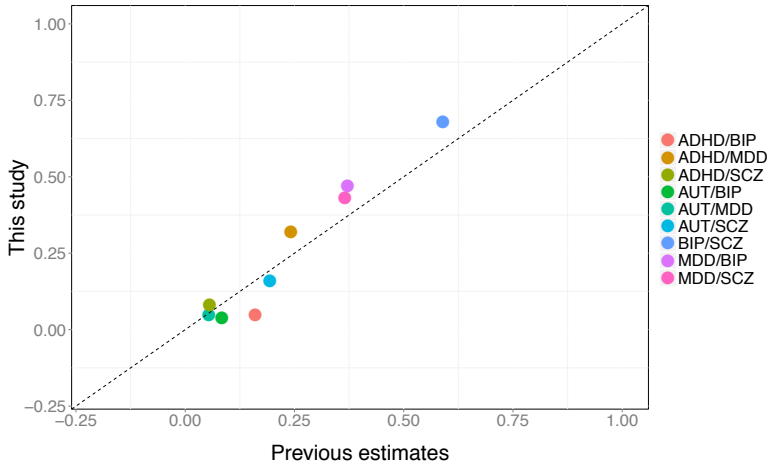
Supplementary data

A. Heritability



B. Genetic correlations



C. SNP-coheritability

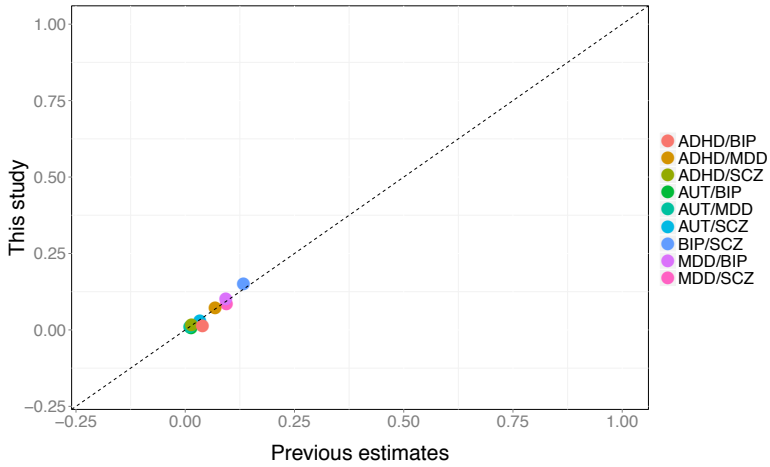


Figure S1. Previous estimates (Lee et al. 2013) plotted against estimates from this study for 5 psychiatric disorders. Both studies and the previous utilised the same data. However, the previous estimates used a bivariate model and so overlapping and closely related samples were excluded on a pairwise basis. In this study overlapping

samples and closely related samples were removed across all 5 disorders generating small samples per disease. A. SNP-heritability (correlation coefficient between previous and current estimates = 0.69); B. Genetic correlations (correlation coefficient between previous and current estimates = 0.98); C. SNP-coheritability (correlation coefficient between previous and current estimates = 0.98)

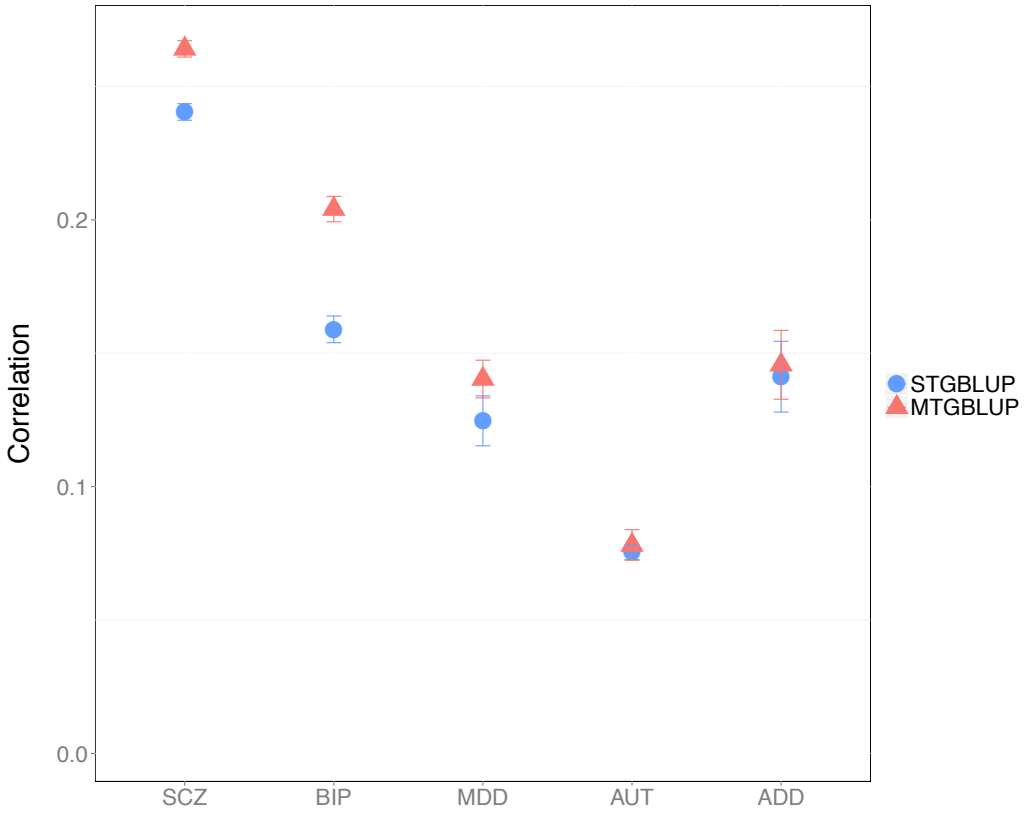
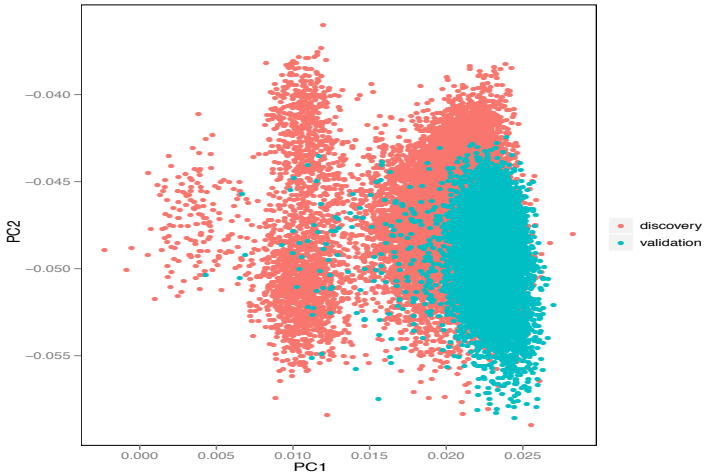
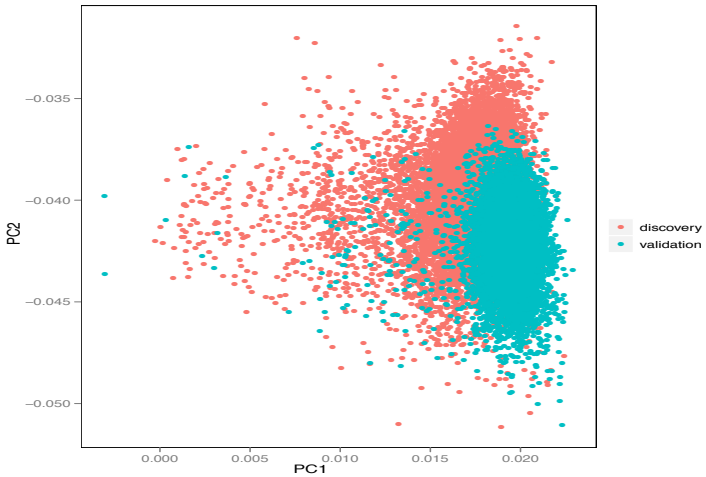


Figure S2. Prediction accuracy of MTGBLUP and STGBLUP for five psychiatric disorders in the within-study validation of PCG. Results are based on 5 replicates Error bars are ± empirical standard error. Prediction accuracy is measured as the mean of the correlation coefficient between the true disease status and the predicted genomic risk score in the validation data.

A. Schizophrenia



B. Bipolar disorder



C. Major depressive disorder

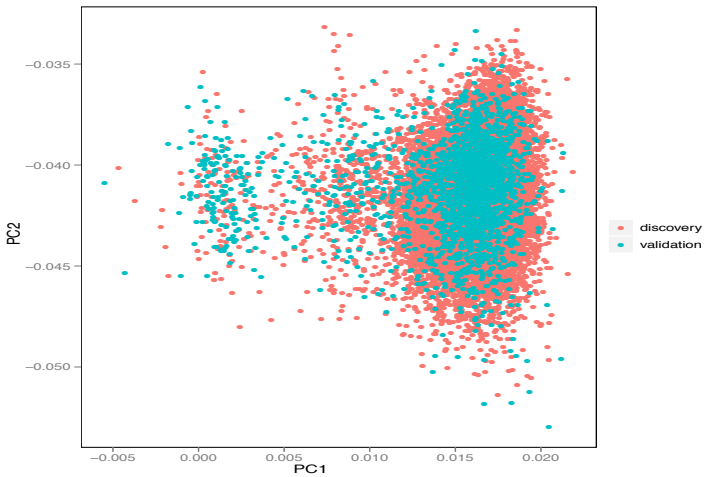
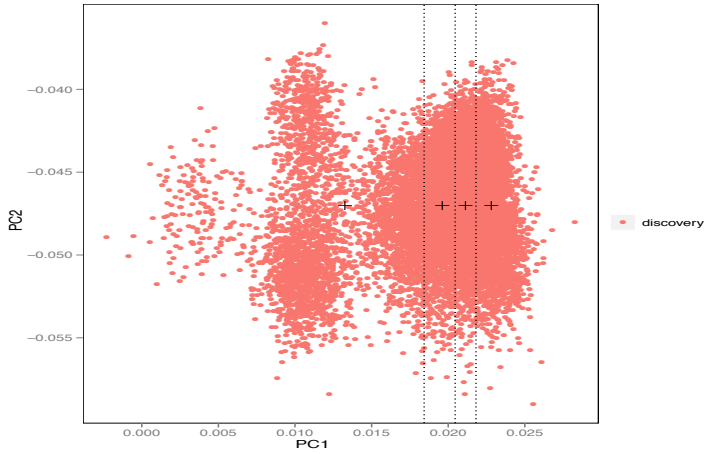
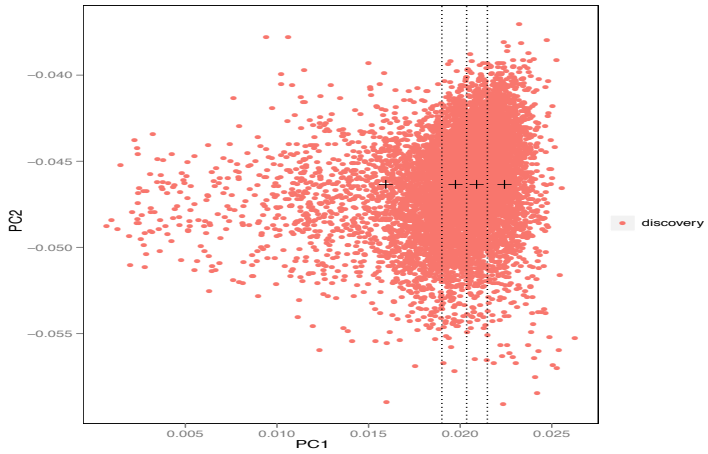


Figure S3. Principal component analysis based on the projected PC from POPRES for SCZ (A), BIP (B) and MDD (C). The same SNPs were selected from the discovery and validation set and used to project PC in each disorder. The number of SNPs used was 745,631 for SCZ, 645,237 for BIP and 673,109 for MDD.

A. Schizophrenia



B. Bipolar disorder



C. Major depressive disorder

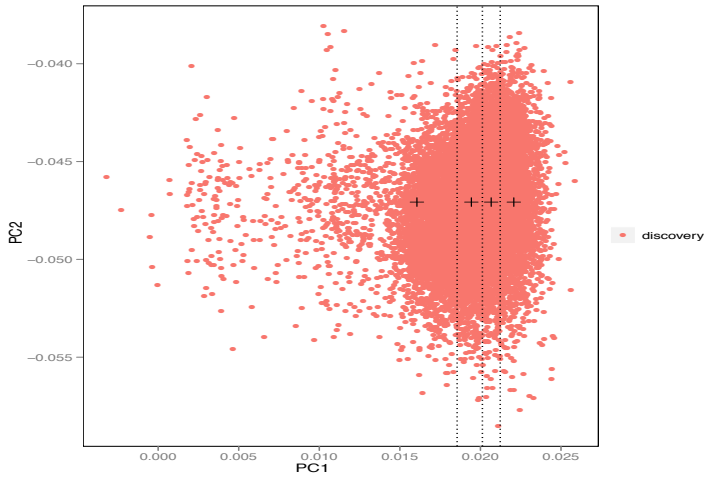
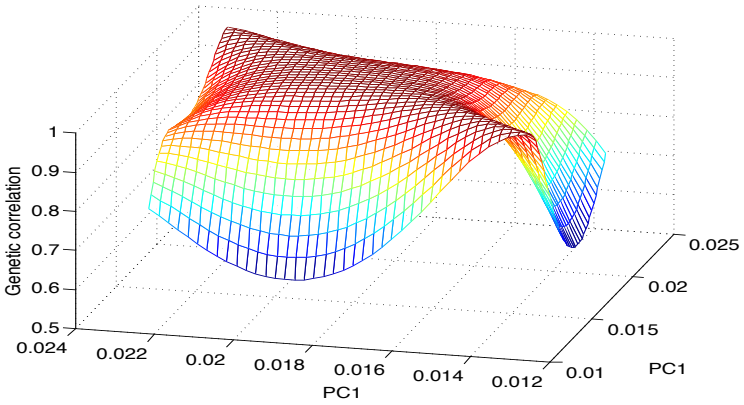
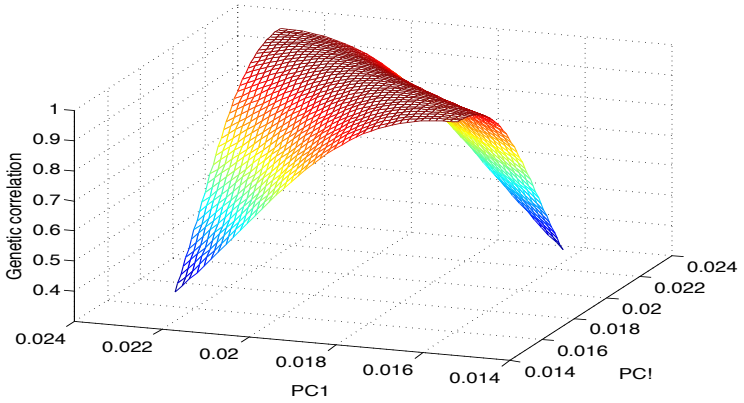


Figure S4. Principal component analysis based on the projected PC from POPRES for the discovery sample of SCZ (A), BIP (B) and MDD (C). The number of SNPs used to project PC was 745,705 for all three disorders. The dashed lines are 25%, 50% and 75% quartiles of the first principal component in the discovery sample (four population classes) and the plus sign is the mean (of PC1) of each population class. The four population classes for each trait were used in the reaction norm model (Appendix B).

A. Schizophrenia



B. Bipolar disorder



C. Major depressive disorder

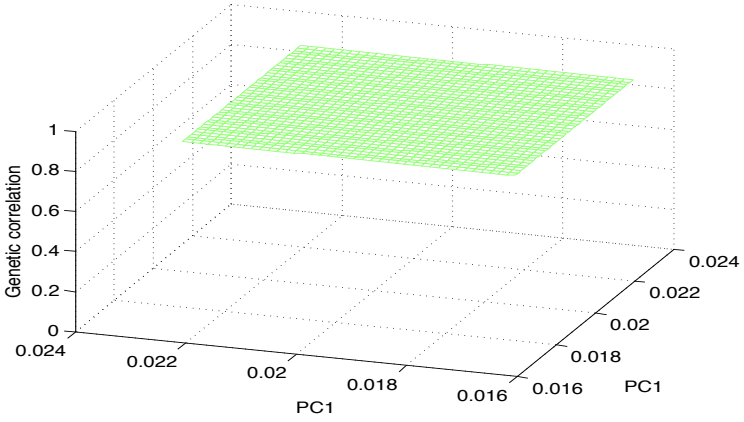
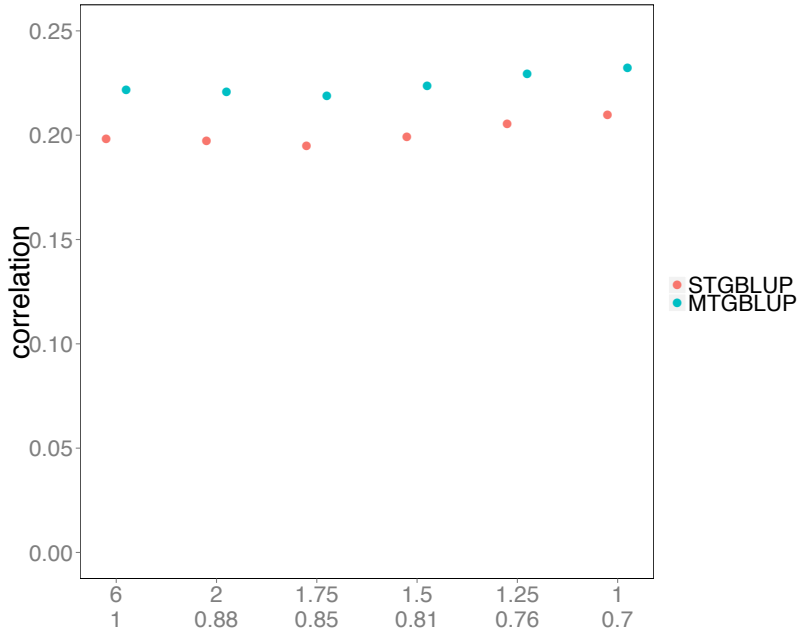
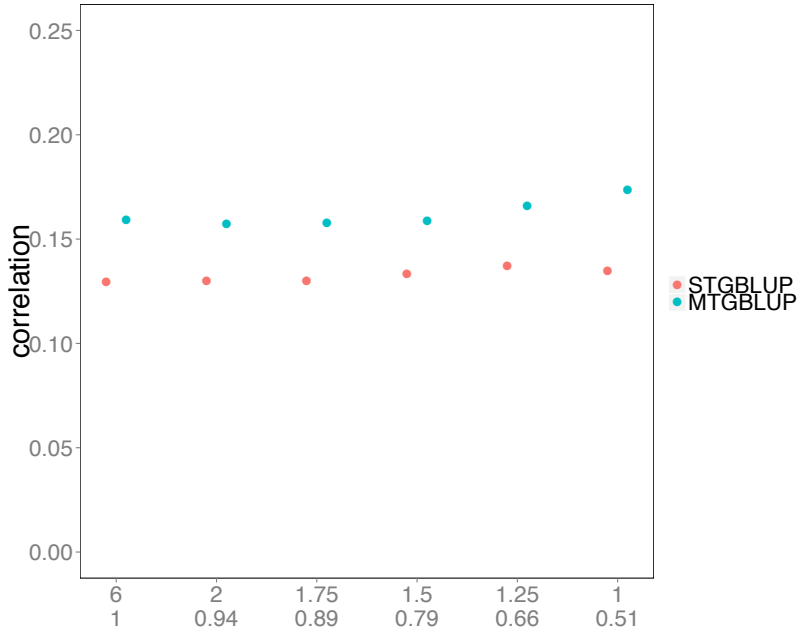


Figure S5. Genetic correlation pattern across different ancestry principal components estimated from the reaction norm model (Appendix B). Order of polynomial (see Table S9): A. k=3 for SCZ, B. k=2 for BIP, C. k=1 for MDD.

A. SCZ


0.25
0.20
0.15
0.10
0.05
0.00
correlation
STGBLUP
MTGBLUP
6
1
2
0.88
1.75
0.85
1.5
0.81
1.25
0.76
1
0.7
number of standard deviations from mean / fraction included

B. BIP


0.25
0.20
0.15
0.10
0.05
0.00
correlation
STGBLUP
MTGBLUP
6
1
2
0.94
1.75
0.89
1.5
0.79
1.25
0.66
1
0.51
number of standard deviations from mean / fraction included

C. MDD

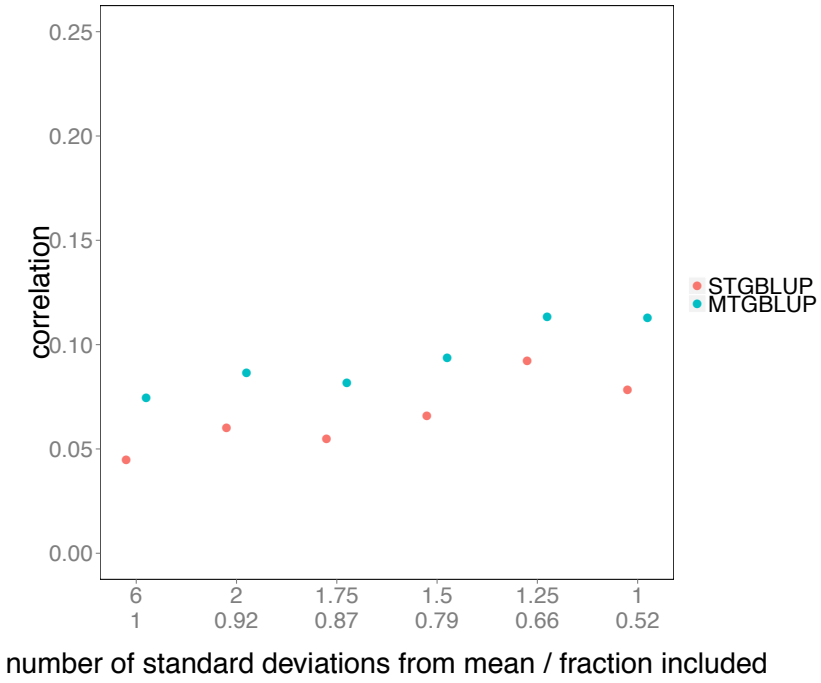


Figure S6. Effect of excluding population outliers on the prediction accuracy from MTGBLUP and STGBLUP. Outliers are defined as points ± 6, 2, 1.75, 1.5, 1.25 and 1 SD from the mean for both the first and second principal components in the independent (A) SCZ, (B) BIP, (C) MDD samples.

Table S1. Comparison of prediction accuracy (Correlation) and regression coefficient (Regression) from MTGBLUP and STGBLUP for five psychiatric disorders in the within-study validation of PCG

	Correlation	Regression
	Schizophrenia	
STGBLUP	0.240 (0.003)	1.011 (0.022)
MTGBLUP	0.264 (0.003)	1.019 (0.019)
	Bipolar disorder	
STGBLUP	0.159 (0.005)	1.091 (0.054)
MTGBLUP	0.204 (0.005)	0.971 (0.025)
	Major depression	
STGBLUP	0.125 (0.009)	1.078 (0.054)
MTGBLUP	0.140 (0.007)	0.930 (0.038)
	Autism Spectrum Disorders	
STGBLUP	0.075 (0.003)	0.965 (0.080)
MTGBLUP	0.078 (0.006)	0.884 (0.054)
	ADHD	
STGBLUP	0.141 (0.013)	1.144 (0.052)
MTGBLUP	0.146 (0.013)	1.116 (0.050)

Correlation and regression coefficients and empirical standard errors (in brackets) are calculated based on 5 replicates.

Table S2. Prediction accuracy for schizophrenia (SCZ), bipolar disorder (BIP) and major depressive disorder (MDD) in independent validation data sets when using the second annotation model.

	Correlation			Regression		
	SCZ	BIP	MDD	SCZ	BIP	MDD
STGBLUP-SAI	0.199	0.130	0.048	0.787	0.746	0.323
MTGBLUP-SAI	0.222	0.160	0.076	0.817	0.718	0.470

MTGBLUP-SAI or STGBLUP-SAI: in the SAI model SNPs are grouped into schizophrenia / autism / intellectual disability (SAI) candidate genes sets. Prediction accuracy is given as the correlation coefficient between the true disease status and the predicted genomic risk score in the validation data.

Table S3. Comparison of the fit of standard model with the SAI-annotation model for STGBLUP, MTGBLUP and MTGBLUP.

		SCZ	BIP	MDD
x_1	x_2	p-values from LRT		
STGBLUP	STGBLUP-SAI	0.18	0.18	0.070
MTGBLUP	MTGBLUP-SAI	0.22	0.71	0.54
STGBLUP	MTGBLUP-SAI	1.2e-24	9.7E-15	0.0083

Likelihood ratio LR = -2 [logL(x_1) - logL(x_1+ x_2)]

Table S4. SNP-heritability and genetic correlation between discovery and validation set from bivariate analyses for SCZ, BIP and MDD

Trait 1/ trait 2	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	p-value
SCZ discovery/ SCZ validation	8826/ 4068	6106/ 5471	0.23 (0.01)	0.21 (0.02)	0.80 (0.05)	7.3E-51
BIP discovery/ BIP validation	5867/ 2029	3328/ 5338	0.21 (0.02)	0.22 (0.02)	0.75 (0.08)	7.3E-17
MDD discovery/ MDD validation	8770/ 822	6506/ 467	0.28 (0.02)	0.11 (0.25)	0.51 (0.64)	0.84

h^2 is SNP-heritability on the liability scale. r_g is genetic correlation between discovery/validation set. P-value is for testing if r_g is different from 1, indicating heterogeneity for a lower p-value.

Table S5. Reaction norm model to test heterogeneity across populations classified by the first ancestry principal component

Polynomial order k	log L	Number of parameters	LR	p-value
SCZ				
1	3830.01	5	0.00	1
2	3836.61	7	13.20	0.0014
3	**3840.55**	**10**	**21.07**	**0.00078**
4	3841.36	14	22.69	0.0069
BIP				
1	2342.89	5	0.00	1
2	**2349.27**	**7**	**12.76**	**0.0017**
3	2351.64	10	17.49	0.0037
4	2352.77	14	19.75	0.019
MDD				
1	**3326.17**	**5**	**0.00**	**1**
2	3326.39	7	0.42	0.81
3	3328.24	10	4.14	0.53
4	3330.98	14	9.61	0.38

Populations are classified by the first ancestry principal component. Schizophrenia (p-value=0.00078) and bipolar disorder (p-value=0.0017) show a significant evidence for heterogeneity across different populations.

Table S6. Additional required sample size of STGBLUP to achieve the same prediction accuracy as MTGBLUP and MTGBLUP-CNS.

	SCZ	BIP	MDD
MTGBLUP	4660 (3110 – 6270)	5550 (2830 – 8640)	10940 (730 – 24440)
MTGBLUP-CNS	5080 (3520 – 6690)	6220 (3380 – 9380)	11550 (1220 – 25300)

Values in brackets are Ninety-five precent confidence interval (CI) is in bracket.

Table S7. Comparison of prediction accuracy (correlation) and regression coefficient (regression) from bivariate GBLUP (BVGBLUP)

model	Dependent variable	correlation	regression
BVGBLUP (SCZ, BIP)	SCZ	0.220	0.822
BVGBLUP (SCZ, BIP)	BIP	0.156	0.705
BVGBLUP (SCZ, MDD)	SCZ	0.201	0.785
BVGBLUP (SCZ, MDD)	MDD	0.071	0.461
BVGBLUP (BIP, MDD)	BIP	0.133	0.682
BVGBLUP (BIP, MDD)	MDD	0.040	0.263

Table S8. Results of model comparison between bi-variate (BVGBLUP) and multi-trait GBLUP (MTGBLUP).

x1	x2	Dependent variable	p-value
BVGBLUP (SCZ, BIP)	MTGBLUP	SCZ	1.9E-03
BVGBLUP (SCZ, BIP)	MTGBLUP	BIP	7.4E-03
BVGBLUP (SCZ, MDD)	MTGBLUP	SCZ	1.9E-23
BVGBLUP (SCZ, MDD)	MTGBLUP	MDD	0.50
BVGBLUP (BIP, MDD)	MTGBLUP	BIP	2.5E-14
BVGBLUP (BIP, MDD)	MTGBLUP	MDD	0.00056

Likelihood ratio LR = -2 [logL(x1) - logL(x1+x2)]

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