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Figure 1. Miami plot depicting our BD GWAS (top) and MDD GWAS (bottom) based on our non-overlapping sample, overlaying loci with P < 1e-06 from different GWAS, as well as common loci: Red – BDvsMDD GWAS, Blue – CC-GWAS, Yellow – Meta-analysis, Green – Common locus between Meta-analysis and CC-GWAS (1 in total), Purple – Common loci between Case-Case GWAS and CC-GWAS (3 in total), Orange – Common loci between all three methods (1 in total). Within each locus, only SNPs in LD (R2>0.1) with the index SNP are coloured, in order to accurately display the underlying signal in both the top and bottom panels. The two genome-wide significant loci (for the Meta-analysis and CC-GWAS) are labeled with their index SNP. The BDvsMDD GWAS (red) column on chromosome 11 consists of two neighboring but non-overlapping loci. Meta-regression was excluded from this figure due to low power. Region plots for all highlighted loci are shown in Supp. Figures 6a-f. SNPs within common loci are coloured accordingly in Supp. Tables 6 and 7.

Figure 2. A) Genetic correlations between the different GWAS methods performed B) Genetic correlations between the case-case GWAS (BDvsMDD purple), our BD case-control GWAS (blue) and our MDD case-control GWAS (red) on the y-axis and GWAS of other psychiatric traits from the PGC on the x-axis.

Figure 3. Ability of our GWAS to distinguish BD vs. MDD status in our cohorts: Area under the ROC curve (AUC) of PRS analysis using SBayesR for the BDvsMDD GWAS (A) using all BD vs. MDD cohorts as target and (B) using BD with depressive onset (BD-D) vs. MDD cohorts as target; (C) Ability of different psychiatric traits from the PGC to classify BD vs. MDD status in our cohorts (mean AUC weighted by cohort effective sample size is reported).

Table 1. Replication results of PRS analysis using iPSYCH as the target cohort. Top panel: AUC and Nagelkerke’s R2 achieved by each model (i.e. null model - principal components only, full model - BDvsMDD GWAS and full model with combined predictor) for BD vs. MDD status classification; bottom panel: similar for BD-D vs. MDD status.

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Supplementary Figure 1. PCA plots for each cohort, showing PCA1 (x-axis) against PCA2 (y-axis), corresponding to the case-case PCA (A) and the case-control (B) analysis.

Supplementary Figure 2. Manhattan plots for the BDvsMDD GWAS (A), the BD-DvsMDD GWAS (B), the meta-regression GWAS (C) and the CC-GWAS (D).

Supplementary Figure 3. Quantile-quantile plots for the BD vs. MDD GWAS (A), the BD-DvsMDD GWAS (B), the meta-regression GWAS (C) and the CC-GWAS (D).

Supplementary Figure 4. Region plots for the BD vs. MDD GWAS (A), the meta-regression GWAS (B) and the CC-GWAS (C).

Supplementary Figure 5. Region forest plots for the BD vs. MDD GWAS.

Supplementary Figure 6. Region plots for all highlighted regions in Figure 1. (A) Regions identified by the BDvsMDD GWAS only (red). (B) Regions identified by CC-GWAS only (blue). (C) Regions identified by the meta-analysis only (yellow). (D) Regions identified by the BDvsMDD GWAS and CC-GWAS (purple). (E) Regions identified by the meta-analysis and CC-GWAS (green). (F) Region identified by all three methods (orange). For this region the selected index SNPs is not present in CC-GWAS and has been substituted with its closest LD proxy (R2=0.799).

Supplementary Figure 7. Nagelkerke’s R2 of PRS analysis using SBayesR for the BD vs. MDD GWAS (A) and the BD-D vs. MDD GWAS (B) for all cohorts.

Supplementary Figure 8. Comparison of classification accuracy between the PRS predictors based on the BD vs. MDD GWAS (BDvsMDD - red), the BD GWAS (BD - dark blue) and the BD GWAS with its sample size made equal to the BD vs. MDD GWAS (BD-subN, light blue). A) AUC with the BD vs. MDD cohorts as target, B) Ng R2 with the BD vs. MDD cohorts as target, C) AUC with the BD-D vs. MDD cohorts as target, D) Ng R2 with the BD-D vs. MDD cohorts as target.

Supplementary Figure 9. Comparison of PRS predictors based on our BD vs. MDD GWAS (blue), our combined predictor (magenta), the latest PGC BD GWAS (orange), and a predictor based on the combination of the two predictors based on our BD vs. MDD GWAS and the PGC BD GWAS (yellow). AUC with cohort “grp5\_neth” as target is reported.

Supplementary Figure 10. Comparison of combination of PRS predictors based on our GWAS: BDvsMDD GWAS + BD GWAS (blue), BDvsMDD GWAS + MDD GWAS (red) and full predictor combining all BDvsMDD GWAS + BD GWAS + MDD GWAS (gray). A) AUC for all BD cases vs. MDD, B) Ng R2 for all BD cases vs. MDD, C) AUC for BD-D vs. MDD, D) Ng R2 for BD-D vs. MDD.

Supplementary Table 1. Merging and quality control results for case-case cohorts: constituent case-control cohorts for each of the 13 grouped case-case cohorts are reported, together with pre- and post-QC number of cases for each disorder and number of SNP.

Supplementary Table 2. Description of our quality control procedure with flags and corresponding values.

Supplementary Table 3. Summary of results introducing controls to the 13 grouped cohorts: Post-QC number of cases for both disorders as well as control individuals, inflation factor lambda, as well as number of post-QC SNPs are reported.

Supplementary Table 4. Full list of CC-GWAS input parameters used. Heritability estimates were obtained from LDSC.

Supplementary Table 5. List of genome-wide significant loci (P<5x10e-08) and suggestive hits (P<1x10e-4) for all different GWAS methods: (a) case-case BD vs. MDD, (b) meta-regression, (c) CC-GWAS and (d) meta-analysis. For the CC-GWAS hit, the corresponding statistics for other GWAS are reported as well (e).

Supplementary Table 6. List of all SNPs with P < 1e-04 and their positional annotation (using FUMA): (a) case-case BD vs. MDD, (b) meta-regression, (c) CC-GWAS and (d) meta-analysis.

Supplementary Table 7. List of all SNPs with P < 1e-04 with eQTL annotation (using FUMA, restricted to brain-related tissues): (a) case-case BD vs. MDD, (b) meta-regression, (c) CC-GWAS and (d) meta-analysis.

Supplementary Table 8. Summary of the number of loci retrieved by the mtCOJO method compared to the total number of loci identified by each of our GWAS methods.

Supplementary Table 9. List of hits from the “reverse-GWAS” analysis from Coleman et al. 2020: results from our case-case BD vs. MDD are reported.

Supplementary Table 10. List of pathways that reach nominal significance for enrichment using MAGMA: (a) case-case BD vs. MDD, (b) meta-regression, (c) CC-GWAS and (d) meta-analysis.

Supplementary Table 11. List of genetic correlations between our GWAS and GWAS of other psychiatric traits from the PGC.

Supplementary Table 12. Paired t-test comparing the classification accuracy of models based on our PRS predictors against the null model based on principal components only.