Identifying genetic differences between bipolar disorder and major depression through multiple GWAS

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Abstract

Background: Accurate diagnosis of bipolar disorder (BD) is difficult in clinical practice, with an average delay between symptom onset and diagnosis of about 7 years. A key reason is that the first manic episode is often preceded by a depressive one, making it difficult to distinguish BD from unipolar major depressive disorder (MDD).

Aims: Here, we use genome-wide association analyses (GWAS) to identify differential genetic factors and to develop predictors based on polygenic risk scores that may aid early differential diagnosis.

Methods: Based on individual genotypes from case-control cohorts of BD and MDD shared through the Psychiatric Genomics Consortium, we compile case-case-control cohorts,

applying a careful merging and quality control procedure. In a resulting cohort of 51,149 individuals (15,532 BD cases, 12,920 MDD cases and 22,697 controls), we perform a variety of GWAS and polygenic risk scores (PRS) analyses.

Results: While our GWAS is not well-powered to identify genome-wide significant loci, we find significant SNP-heritability and demonstrate the ability of the resulting PRS to distinguish BD from MDD, including BD cases with depressive onset. We replicate our PRS findings, but not signals of individual loci in an independent Danish cohort (iPSYCH 2015 case-cohort study, N=25,966). We observe strong genetic correlation between our case-case GWAS and that of case-control BD.

Conclusions: We find that MDD and BD, including BD with a depressive onset, are genetically distinct. Further, our findings support the hypothesis that Controls – MDD — BD primarily lie on a continuum of genetic risk. Future studies with larger and richer samples will likely yield a better understanding of these findings and enable the development of better genetic predictors distinguishing BD and, importantly, BD with depressive onset from MDD.

1. Introduction

Bipolar disorder (BD) affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status[1,2]. In WHO's World Mental Health surveys, BD was ranked as the illness with the second greatest effect on days out of role[3,4]. Accurate diagnosis of BD is difficult in clinical practice: mean delay between symptom onset and diagnosis is around 7 years[5]. One of the main reasons for this delay is that onset is often characterized by a depressive episode and until the onset of mania it is difficult to distinguish these BD patients from patients with unipolar major depressive disorder (MDD) [6,7,8,9,10,11,12]. For example, in studies that have followed-up patients with an initial MDD diagnosis, approximately between 10-20% demonstrate conversion to BD over follow-up periods of about 5-10 years[13,14]. The misdiagnosis of BD can have significant detrimental consequences, including prescription of antidepressants in the absence of mood-stabilizing drugs, which can lead to mania[15], poor clinical outcomes and ultimately high healthcare costs. Family-based studies[8,16] and our recent GWAS [17] demonstrate independent patterns of inheritance for mania and

depression and initial presentation of bipolar disorder[10]. Several recent studies identified BD genetic liability as a predictor of conversion to BD[18,19]. Together, these findings suggest that scrutinizing the genetic relationship between these two core phenotypes will be valuable in understanding risk for BD. While several summary-statistics-based genetic studies have evaluated genetic similarities and differences between BD and MDD[19], no study has yet been performed directly assessing the genetic differences between these two phenotypes using a systematic approach of combining individual-level genetic data from different cohorts.

Here, we aim to characterize genetic differences between BD patients and patients with MDD using data from the Psychiatric Genomics Consortium (PGC total N=68,612 participants)[20,21] with a replication in the iPSYCH case-control study (total N=25,966)[22,23]. In a follow up analysis, we focus specifically on patients with a first onset of depression, *depression-first BD,* who are most difficult to differentiate from MDD in clinical settings.

2. Methods

2.1. Sample Description

Our analyses are based on 17,673 BD and 14,346 MDD cases of European ancestry from Europe, North America and Australia from the Psychiatric Genomics Consortium (PGC) BD and MDD Working Group, which comprised our discovery data[20,21]. For a list of included cohorts, their sample sizes and case control breakdown, see the Supplementary Material (Supp. Tables 1, 2). The individual studies were approved by the respective local ethics committees and all participants provided written informed consent.

Additionally, summary statistics of GWAS based on ICD-10 secondary care contacts from national health registers[24,25] for both disorders were provided for the iPSYCH case-cohort study[22,23] , which were used for replication. All individuals were born in Denmark between 1981 and 2008 and enrolled based on a secondary care contact recorded in national health registers for BD (ICD-10: F30-F31) or MDD (ICD-10: F32-

F33) before 2016. Individuals with a schizophrenia (ICD-10: F20) diagnosis were excluded. For iPSYCH samples, retrieved from the Danish Neonatal Screening Biobank, parents were informed at the time of sampling and given the option to withdraw the sample from inclusion in research studies[22].

Polarity at onset (PAO) was available for a subset of participants with a BD diagnosis in the PGC cohorts. For these patients, as in our previous study[17], PAO was determined by selecting the earliest age between the onset of mania/hypomania and depression, or as provided by the cohorts. Patients for whom PAO was available were categorized into two subgroups: depression before mania/hypomania (depression-first), and mania before depression of a mixed onset (mania-first). The latter category includes both participants whose onset was marked by an episode with mixed features and participants who had their first manic and depressive episode within the same year.
For the iPSYCH data, depression-first PAO was indirectly inferred based on the presence of a registered MDD contact prior to first registered BD contact.

2.2. Genotype data merge, quality control and imputation

All PGC cohorts in our analysis ascertained patients with a single main diagnosis; either MDD or BD. To perform direct case-case genetic analyses at the genotype level, a first step is to combine multiple independent cohorts into unified cohorts including both MDD and BD case participants. To do so, great care needs to be taken to avoid introducing population stratification and technical artifacts while combining distinct data sources. We developed and applied an iterative procedure for merging, quality control and imputation in Ricopili[26], described in detail in the Supplementary Notes A section. We thereby compiled 13 grouped case-case cohorts including 15,532 BD cases and 12,920 MDD cases in total.
We created a similar set of 13 grouped cohorts, adding 40,160 control participants from the original merged cohorts, performing a similar quality control procedure. The resulting 13 pairs of case-control cohorts contained 14,513 BD cases vs. 22,697 controls and 12,259 MDD cases vs. 17,463 controls, after additional outlier and overlap exclusions.

We also leveraged available information about BD POA (manic episode first - BD-M or depressive episode first - BD-D) to compile 7 case-case cohorts with 2,597 depression-first BD cases (BD-D) and 9,217 matching MDD cases. For BD-M, the sample size was too small (1,300 cases) and the overall observed heritability did not meet the recommended significance criteria (z=2.45, P>0.01)[27], so we have not included the BD-M-based stratification in further analyses.

2.3. Genome wide association analyses

To evaluate genetic differences between BD and MDD, we performed three primary GWAS analyses and one replication analysis:

2.3.1. Genotype-based Case-Case GWAS Meta-analysis

To identify genetic risk factors differentiating BD and MDD, we first compare BD and MDD cases directly, similar to a previous comparison of schizophrenia to BD[28]. Specifically, we perform GWAS on each of the 13 grouped case-case cohorts based on dosage genotypes, followed by standard inverse-SE weighted meta-analysis across all grouped cohorts, whereby individuals with BD were coded as cases, MDD cases as controls. The first 20 principal components were used as covariates. We refer to this primary GWAS analyses as *BDvsMDD GWAS*. We repeat this analysis using only depression-first BD cases and matched MDD cases (7 case-case cohorts) and refer to it as *BD-DvsMDD GWAS*.

2.3.2. Meta-regression analysis

For this second GWAS analysis we introduce control individuals and aim to identify genetic differences between BD and MDD *relative to controls.* To do so, for each of the 13 cohorts, we first generated summary statistics for two GWAS: one of BD vs. controls and one of MDD vs. controls. Note that the controls for each group are split between BD and MDD cases proportionally (see previous section). We then used a meta-regression approach to model the effect size of each SNP as a function of a single fixed covariate:

a binary indicator of phenotype (BD or MDD, see also Supp. Notes B). This GWAS is referred to as *MetaRegr GWAS.*

We also performed separate random effects meta-analyses of the BD and MDD GWAS summary statistics to evaluate which phenotype appeared to have more heterogeneity in SNP effect sizes using the respective meta-regression τ^2 estimates.

2.3.3. CC-GWAS

We also performed a GWAS based on the CC-GWAS method[29], using BD vs. controls and MDD vs. controls summary statistics. For this, we compiled a version of our grouped cohorts based on a set of completely overlapping controls, as CC-GWAS covariance matrix estimation benefits from control overlap. LD score regression [30] was used to calculate the set of parameters required as input by the method (see Supp. Table 4). In addition to applying a genome-wide threshold for p-value, CC-GWAS includes an "stress test" to determine whether a SNP is considered significant, accounting for any indication of differential tagging of a shared causal allele (i.e. SNPs with similar allele frequency for both disorders), arising from subtle ancestry differences in the input. We thus also filter our results accordingly, including hits which pass this additional filter.

2.3.4 Reverse GWAS

In Coleman et al.[31], summary statistics were used to identify loci with differential signals between the two disorders ("reverse-effect" analysis). We evaluated concordance between loci identified through this analysis and our results, by evaluating the genome-wide significant hits in the "reverse-effect" analysis (three in total) in our three GWAS.

2.3.5. Replication analysis with iPSYCH

To replicate our findings from the BDvsMDD GWAS, we performed a similar case-case association analysis in the iPSYCH 2015 case-cohort study (2,524 BD cases and 23,442 MDD cases). GWAS was performed using Plink2 v2.00a2[32] in two independent

samples (iPSYCH-2012, N_BD=1,452, N_MDD=15,920 and additional iPSYCH-2015i, N_BD=1,072, N_MDD=7,522) and meta-analyzed.

For our onset analysis, we also utilize a constrained set of 976 individuals who had an MDD diagnosis registered on the same day or prior to their BD diagnosis (BD-D), against the set of 23,442 individuals with MDD diagnosis.

To evaluate the degree of replication of LD independent index SNPs from our primary GWAS, we performed a sign test, grouping variants with p-value smaller than 1e-05, to determine whether the percentage of variants in the original analysis retaining their direction of effect in the replication analysis is significantly higher than chance.

2.4. Heritability and genetic correlation

For all GWAS, heritability and genetic correlations were estimated with LD score regression. In addition, we estimated genetic correlations between our GWAS and well-powered (SNP heritability z-score>5 and more than 10,000 cases) psychiatric GWAS made publicly available by the PGC (https://pgc.unc.edu/for-researchers/download-results/). The following traits were included: Schizophrenia (SCZ), ADHD, Cannabis Use Disorder (CUD), Alcohol Dependence (AD), Alcohol Use Disorder (AUD), Anorexia Nervosa (AN), Autism Spectrum Disorder (ASD), Post-traumatic Stress Disorder (PTSD). Since our analysis is currently limited to European ancestry, we used summary statistics limited to the European population subset.

2.5. Polygenic score analyses

To evaluate whether our GWAS can help distinguish between patients with MDD and those with BD on an individual level, we compute polygenic risk scores (PRS). We calculate leave-one-out (LOO) summary statistics based on our set of GWAS and use SBayesR[33] to calculate polygenic scores for each of the 13 grouped cohorts respectively. We thus create a number of different polygenic predictors, including combinations of those using multiple regression. We report the area-under-curve (AUC) score as a metric for performance, as well as the percentage of variance explained, expressed in terms of Nagelkerke's R^2.

Specifically, we calculate polygenic scores based on summary statistics of 4 different GWAS: i) BDvsMDD GWAS, ii) BD vs. controls GWAS (BD GWAS), iii) MDD vs. controls GWAS (MDD GWAS) and iv) MetaRegr GWAS. We compare the ability of each of these scores, based on different GWAS designs, as well as a combination of (i), (ii) and (iii) (combined using multiple regression), to predict the target phenotype, namely to classify BD vs. MDD status.

To obtain within-cohort standard errors and calculate confidence intervals for the AUC, we bootstrap the process based on 100 samples for each cohort.

To compare classification performance across different predictors, we further performed paired (across cohorts) weighted t-tests, with weights based on the effective sample size of the target cohorts, to determine the statistical significance of the difference in performance between individual predictors and the combined predictor (CC+BD+MDD). Since using t-tests we do not rely on confidence intervals, these performance comparisons between predictors were based on the AUC values reported for each of our cohorts, and not the ones obtained via the bootstrapping process.

To further quantify the impact of sample size, we compared our predictors to the BD GWAS of the Psychiatric Genetics Consortium in [34]. As each of our grouped cohorts contains multiple BD and MDD studies, it is an involved process to create LOO summary statistics while removing overlap; we therefore limit this comparison to one cohort (“grp5_neth”).

Since we are most interested in distinguishing BD patients with an onset of depression from those with unipolar MDD, we repeat the above analysis using BD-D vs. MDD cohorts as target datasets.

Finally, we test the reproducibility of our PRS results on the iPSYCH cohort.

2.6. Polygenic risk scores based on other psychiatric traits

Using SBayesR, we also calculated polygenic scores based on public summary statistics for each of the psychiatric GWAS included in our genetic correlation analysis. We report mean weighted AUC calculated across our 13 cohorts.

3. Results

3.1. GWAS does not identify significant loci

Our GWAS results using our three different GWAS methods are summarized in Supp. Table 5, after visual inspection of region plots produced by Ricopili for reasonable LD patterns. Overall, we observe no genome-wide significant hits for BDvsMDD or meta-regression, while one locus passes the genome-wide threshold for CC-GWAS. While our primary GWAS (BDvsMDD) did not yield significant loci, we observed significant heritability (observed h2 = 0.23 (se 0.02), intercept 1.001 (se 0.01)). For the BD-D vs. MDD GWAS, we observed similar results (observed h2 = 0.18 (se 0.04), intercept 1.01 (0.01)). Our two secondary GWAS (meta-regression, CC-GWAS) were strongly correlated with BDvsMDD and with each other (rg 0.91-1, Figure 1a), but they were less well-powered than BDvsMDD (meta-regression: h2 = 0.05 (se 0.01) with intercept 0.96 (0.01), CC-GWAS: h2 = 0.17 (se 0.01) with intercept 0.98 (0.01)).

A total of eight loci reached a suggestive p-value of less than 1e-06 (Supp. Table 5) in BDvsMDD, two of which, marked in bold face, fall within known BD loci [34]. The Manhattan, quantile-quantile (Q-Q), region and region forest plots for this analysis as well as the corresponding Manhattan and QQ plots for the BP-D vs. MDD GWAS can be found in Supp. Figures 2a-b, 3a-b, 4a and 5. As seen in the region plots (Supp. Figure 4a), one of the loci (in chromosome 11) harbors two potentially independent signals.

Respectively, four loci reached suggestive genome-wide significance for the meta-regression analysis, none of which coincide with those of the BDvsMDD GWAS (Supp.

Figures 2c, 3c and 4b). For CC-GWAS, we do not report suggestive loci, since we do not have differential tagging information for those.

For the single hit (rs174601 on chromosome 11, P=6.43e-09, with OR 0.99) identified through this analysis, we also report results on BDvsMDD, BD, MDD and meta-regression (Supp. Figures 2d, 3d and 4c). For both BDvsMDD and meta-regression we observe a similar effect P<1.0e-05 and a larger effect size (OR of 0.93 for BDvsMDD GWAS and 0.89 for meta-regression), while for BD this SNP is genome-wide significant with P = 8.0e-10 and maps onto a known BD locus, close to the FADS1 gene[34]. We observe a signal in the same direction for MDD, though the effect is not significant (P>0.1).

In none of the three different GWAS do we observe genetic signal (at P < 1e-04) for the three SNPs reported to differentiate BD and MDD in [31] (Supp. Table 6).

The phenotype-specific meta-regression analysis allowed us to compare effect size heterogeneity between MDD and BD cohorts. We observed slightly elevated effect size heterogeneity in MDD cohorts compared to BD, indicating that across all SNPs tested, MDD cohorts are slightly more heterogeneous; however, the observed difference is minimal (mean τ^2 values of 3.0e-02 for MDD vs. 2.6e-02 for BD, P<1.0e-16 paired t-test in all 6.9 million SNPs).

3.2. Heritability and genetic correlation indicates a strong correlation with PGC BD GWAS

We observe a strong genetic correlation between the BDvsMDD GWAS summary statistics and the GWAS of PGC BD: rg = 0.95 with BD[20] (Figure 1a and b), primarily BD type I (Figure 1b n; Note that genetic correlation estimates above 1 between PGC analyses occur. These may be due to overlapping individuals in the studies involved.) The correlation between BDvsMDD GWAS and our BD GWAS, using only matched individuals, is also strong: rg = 0.88 (se 0.03). On the other hand, the correlation estimate with PGC MDD[21] is negative rg = −0.05 (se 0.06), but the standard error overlaps with zero. The negative direction of effect is expected, given that MDD cases

were coded as "controls" in our case-case analyses (where "cases" correspond to individuals with BD).

Genetic correlations with other psychiatric traits tracks are presented in Figure 1b, alongside BD and MDD (See also Supp. Table 7). Mostly, the observed genetic correlations follow an expected pattern that matches the observations above: When a trait is strongly correlated with BD, and less so with MDD (e.g., SCZ), the genetic correlation of BDvsMDD falls in between. When a trait is strongly correlated with MDD, and less so with BD (e.g., PTSD, ADHD), the genetic correlation of BDvsMDD is driven towards zero (or a negative correlation) due to the relative strength of the MDD signal. An exception to this "rule" is Alcohol Use, which is more strongly correlated with BDvsMDD (rg=0.19, se=0.05) than with PGC BD (rg=0.09, se=0.04), indicating that genetic risk factors for alcohol use could represent additional independent risk for conversion from MDD to BD.

3.3. Polygenic risk scores can distinguish between MDD and BD, including BD-D.

Figure 2A shows the classification score in terms of AUC (see also Supp. Figure 6 for Nagelkerke's R^2) for all 13 grouped cohorts, for polygenic scores based on BDvsMDD GWAS (BDvsMDD), BD GWAS (BD), MDD GWAS (MDD) and a combination of these three predictors (BDvsMDD+BD+MDD). The mean AUC (over 100 bootstrapped samples per cohort), weighted by cohort sample size is 0.62 (2.29% adjusted Nagelkerke R^2), 0.63 (R^2 = 4%), 0.59 (R^2 = 0.29%) and 0.64 (R^2 = 4.56%) respectively. Similar results are shown on Figure 2B for depression-first BD, as discussed later. For all cohorts in both plots, it can be deduced from the standard error bars that the AUC is significantly higher than chance level (0.5) and also significantly higher than the bootstrapped model using principal components only (null model – AUC of 0.58), with the exception of the MDD; here, the confidence intervals overlap the null model (for AUC) or zero (for adjusted R^2) in seven cohorts. However, using paired t-tests, weighted by effective sample size, we show that the weighted mean across all 13 cohorts is significantly higher than that of the covariates-only "null" model (see Supp. Table 8).

Interestingly, the BD predictor outperforms the predictor built on BDvsMDD cohorts. However, this is likely due to differences in sample size of the underlying GWAS: when

we compare the BDvsMDD predictor to a version of the BD predictor based on a GWAS of equal sample size (BD-subN, see Supp. Notes C, Supp. Figure 7), the performance difference initially observed is no longer significant (p = 0.28 for equal sample size, paired weighted t-test).

Our comparison of the BD and BDvsMDD predictors to a more recent PGC BD collection[34], including 41,917 cases and 371,549 controls, while attempted only for cohort "grp5_neth", demonstrates the power advantage of the PGC BD GWAS-based predictor in classification performance (13.15% R^2 for the PGC BD predictor, compared to 7.16% for the BDvsMDD predictor and 10.98% for our combined BDvsMDD+BD+MDD predictor, Supplementary Figure 8). However, combining our BDvsMDD predictor with the PGC BD one, yields even better performance (R^2 = 14.81%), thus confirming the value of utilizing a predictor based on case-case GWAS.

Using a paired weighted t-test (one-tailed), we observed significantly increased performance of the combined predictor relative to each of the individual predictors: mean weighted AUC BDvsMDD = 0.60, BD = 0.62, MDD = 0.5 and combined = 0.63 (P-value of 3.5e-05 (BDvsMDD), 1.9e-03 (BD) and 6.5e-07 (MDD)).

To delineate the contribution of the signals attributable to each disorder, we further broke down the combined predictor to two-way combinations and found that the MDD signal contributes little orthogonal signal to the BDvsMDD+BD combination: mean AUC 0.62 for BDvsMDD+BD (compared to 0.63 for BDvsMDD+BD+MDD, as mentioned above, with P = 0.04, see Supplementary Figure 9A,B).

We next limited our analysis to the subgroup of patients with depression onset, testing the ability of BDvsMDD (and BD and MDD) PRS to distinguish between depression-first BD cases (BD-D) and MDD cases. We found that the classification accuracy is similar to that including all BD cohorts (Figure 2B and Supplementary Figure 9C,D). Our available sample size did not permit a similar analysis for manic-first episode BD (heritability z-score of 2.4).

Finally, Figure 3 shows the classification performance of all different psychiatric traits listed above (see Methods) with respect to differentiating between BD and MDD cases. Only SCZ is able to provide substantial differentiation between BD and MDD, comparable to our BDvsMDD GWAS (AUC = 0.61, se = 0.02), while for the rest of the available psychiatric traits, the performance is very poor.

3.4. Replication with iPSYCH

Sign tests. We tested 39 independent SNPs (P-value < 1.0e-05) from BDvsMDD, of which 22 (56%) had the same direction of effect in discovery and replication samples, indicating an accumulation of the same direction of effect in our replication sample, though this test does not reach nominal significance. We observe minimal SNP heritability of BDvsMDD in the iPSYCH cohort (h2=0.02 (se = 0.02), with intercept 1.003 (0.01)), which may account, in part, for this lack of replication.

Polygenic risk scoring. Polygenic scores based on our full PGC BDvsMDD GWAS, calculated using SBayesR, yielded an AUC of 0.62 and an incremental Nagelkerke R^2 score of 0.40% on iPSYCH, after adjusting for population covariates in the regression model. Although it displays limited power, the PRS predictor is highly significant (P<1.0e-16), and an ANOVA between the full PRS model against the null model using covariates only is significant (P=1.9e-12), confirming the additional classification accuracy conferred by the PRS predictor.

Using our combined predictor in a multiple regression setting yields improved results, with an AUC of 0.63 and adjusted Nagelkerke R^2 of 0.83%. After examination of the individual predictors, we see that the BD predictor has the strongest contribution (P=3.3e-07), while the BDvsMDD and MDD predictors are not statistically significant in the presence of the BD predictor (P>0.1). As before, the full model using BD, MDD and BDvsMDD outperforms the null model using only covariates (ANOVA, P<1.0e-16, also see Table 1) and the model outperforms using the BDvsMDD predictor only (ANOVA, P=2.8e-12).

Constrained to individuals with an MDD diagnosis prior to BD diagnosis, our models have similar classification performance, with an AUC of 0.61 and adjusted Nagelkerke R^2 of 0.32% for the BDvsMDD and an AUC of 0.62 and adjusted Nagelkerke R^2 of 0.69% for the combined predictor.

4. Discussion

With the goal of identifying genetic differences between MDD and BD, we performed three GWAS: a direct comparison between cases of both disorders, a meta-regression testing whether effect sizes differ between BD vs. Controls and MDD vs. Controls across cohorts, and CC-GWAS using case-control summary statistics.

While we found that MDD and BD are genetically distinct, with an estimated heritability of 23% on the observed scale in the direct comparison GWAS (5% by meta-regression, and 17% by CC-GWAS), our primary GWAS yielded no genome-wide significant loci. This lack of signal is likely due to a lack of power. While we were able to include 76% of PGC participants available for these analyses, with the resulting sample sizes they are still relatively underpowered to yield genome-wide significant hits for psychiatric traits, given their polygenicity and sizes of underlying effects, among other factors[35]. Compared to our primary analysis, both secondary GWAS (meta-regression and CC-GWAS), require additional power beyond a standard inverse-weighted meta-analysis, for different reasons. The meta-regression framework benefits from the addition of control individuals, but as a mixed effect model also requires more power to fit additional parameters. On the other hand, CC-GWAS relies solely on summary statistics, which can facilitate access to larger sample sizes as they become available. However, using our data, we obtained one genome-wide significant hit with CC-GWAS, which has support from both BDvsMDD and meta-regression, as well as BD GWAS. The lack of signal in MDD underlines the BD-specificity of this locus.

Somewhat surprisingly, we observed that the BDvsMDD GWAS was strongly correlated with BD GWAS (ranging between 0.88-0.95). Genetic correlations between BDvsMDD and other psychiatric traits are consistent with this observation.

Our leave-one-out polygenic risk scoring analysis confirms the ability of our BDvsMDD GWAS to differentiate between BD and MDD status, which is enhanced when adding multiple predictors from the corresponding case-control GWAS in a multiple regression setting (combined BDvsMDD+BD+MDD predictor). Although it is possible that this is attributable to the increased effective sample size rather than orthogonal signal, we found that the BD and MDD predictors (of similar sample size) contribute differently.

Consistent with the observation that the BDvsMDD GWAS has a high genetic correlation with BD, we found that including the MDD predictor (based on the MDDvsControls GWAS) did not add substantial orthogonal information over and above the BDvsMDD+BD predictors.

Moreover, we observed that our BDvsMDD predictor, which relies on careful matching of cases across cohorts originally designed for case-control studies, does not outperform our BD GWAS predictor, even when the latter, originally of larger sample size, is subsampled for comparison. We did not observe a similar effect for MDD, for which the training GWAS sample size is also larger than the BDvsMDD GWAS: the MDD GWAS was a worse predictor than either the BD GWAS or the BDvsMDD GWAS alone.

Our BDvsMDD and combined predictors had lower performance than a predictor built on the latest BD GWAS[34], which is derived from a much larger sample size, although this comparison was limited to one dataset due to extensive sample overlap between the GWAS being compared. In this dataset, the BD GWAS does not saturate classification accuracy: using our BDvsMDD in conjunction with the well-powered latest BD GWAS from the PGC yielded the highest accuracy for the dataset tested. This is expected, since the overall variance explained by PRS is not yet close to the observed heritability.

Finally, we tested the ability of PRS to differentiate between patients with unipolar depression and BD patients who are most difficult to diagnose: those with a depressive onset. Given that depression-first BD cases have stronger depressive features than those with a manic POA[36,17], one may hypothesize that the ability of PRS to distinguish between depression-first BD cases and MDD cases is lower than that including all BD cases. To the contrary, we observe that the classification accuracy of PRS is statistically indistinguishable to that including all BD patients, in all cohorts. This finding is encouraging, as it opens the possibility of future genetic studies to aid in precision psychiatry efforts, including the differential diagnosis of mood disorders.

Our replication effort in iPSYCH did not show strong signals of replication. This may be due to lack of power, but also may be impacted by the differences in ascertainment

strategies. Patients in the iPSYCH samples are ascertained in secondary care hospitals where only ~15% of MDD cases in Denmark are treated [37], which may mean the PGC MDD cases, comprising our discovery sample, may be less representative of them. This is consistent with previous work[38], showing that the genetic correlation between iPSYCH-PGC for MDD is lower than for BD and that the MDD-BD cross-disorder genetic correlation is higher in iPSYCH than in prior PGC studies, potentially limiting the power to identify discriminating genetic signals. In the PGC data available to us, 83% of BD case participants have BD-I, indicating a selection for severity, whereas this number is not known in iPSYCH. Despite these differences, polygenic risk scores effects were replicated in iPSYCH.

Taken together, our results support the hypothesis that Controls – MDD — BD primarily lie on a continuum of genetic risk, with little specific MDD vs. BD signal detectable at the current sample sizes.
However, larger sample sizes are needed to further investigate the similarities and differences between BD and MDD. Since disease prevalence and heritability differ between BD and MDD (BD has higher heritability and lower prevalence compared to MDD), relatively larger sample sizes are needed to detect MDD-specific signals[39]. Our genetic correlation and PRS results suggest that additional orthogonal signals are yet to be identified.

In addition to larger sample sizes, future studies with richer phenotypic information and multi-diagnostic cohorts, as well as more direct case-case analyses, will likely yield a better understanding of these findings and enable the development of better genetic predictors distinguishing BD from MDD and more specifically depression-first BD from MDD.

Here, leveraging the dataset currently available, we provide an approach to carefully match and compile case-case-control cohorts from existing case-control cohorts, which enable more comprehensive analyses of underlying genetic architecture such as the one provided here. Specifically, the collection of 13 case-case-control cohorts compiled

here will be a valuable resource for the research community in psychiatric genomics. Information on accessing these data from studies shared with the PGC will be available on the PGC website. Summary statistics data from case-case GWAS analysis will also become available upon publication.

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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 hits (P<5x10e-08) and suggestive hits (P<1x10e-6) for all three different GWAS methods: case-case BD vs. MDD, meta-regression and CC-GWAS. For the CC-GWAS hit, the corresponding statistics for other GWAS are reported as well.

Supplementary Table 6. 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 7. List of genetic correlations between our GWAS and GWAS of other psychiatric traits from the PGC.

Supplementary Table 8. Paired t-test comparing the classification accuracy of models based on our PRS predictors against the null model based on principal components only.

Supplementary Notes

A. Merging, Quality Control and Imputation

Using Ricopili[26], we developed and applied the following stringent and iterative procedure to match cohorts based on country and genome chip and perform quality control. We first evaluated potential merges of cohorts with cases of both phenotypes ("case-case" cohorts, with BD coded as "cases" and MDD coded as "controls") based on matched genotyping platform and country. After performing the standard Ricopili QC pipeline, we evaluated each potential match based on nine criteria, to avoid technical artifacts, extremely unbalanced cohorts and inflation due to population structure, as well as to secure adequate number of good-quality variants: 1) the number of SNPs post-QC (fewer than 200,000 not considered) 2) the number of SNPs post-QC per platform (threshold is platform-dependent) 3) and 4) the number of MDD and BD cases (fewer than 100 not considered), 5) the number of participants lost relative to the total sample size (above 10% not considered) 6) number of individuals without phenotype (more than 10 not considered), 7) the ratio of cases failing sex-check (greater than 2.5% not considered) 8) lambda of post-QC GWAS without covariates (greater than 1.2 not considered) 9) number of genome-wide significant SNPs (not considered if any, given the small sample size of individual cohorts). Acceptable values for these criteria on all cohort-merges were obtained by iteratively excluding variants or individuals, while as few cohorts as possible were dropped altogether. We were able to match about 63% of BD cases and 65% of MDD cases of the total PGC collection, grouped into 13 case-case cohorts, and included 15,532 BD cases with 12,920 MDD cases from 22 and 19 cohorts respectively (Suppl. Tables 1, 2).

Principal component analysis of all the final merged cohorts as well as the final QC criteria can be found in Supp. Figures 1a, 1b and Supp. Tables 2 and 3.

Consistent with prior PGC analyses, QC was followed by imputation to the European subset of the Haplotype Reference Consortium (HRC) reference panel[40]. Specifically, genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in EAGLE / MINIMAC3 (with a variable chunk size of 132 genomic chunks and default parameters). The imputation reference set consisted of

54,330 phased haplotypes with 36,678,882 variants from the publically available HRC reference. For subsequent analysis we imposed a filter of INFO>0.8 on imputation quality score.

B. Meta-regression framework

We use a meta-regression approach to model the effect size of each SNP (the coefficient of the SNP from the GWAS) as a function of a single fixed covariate: a binary indicator of phenotype (BD or MDD). Specifically, we used a random-effects meta regression, where group was treated as a random effect. In this random-effects model, a groups's observed effect size $\hat{\theta}_k$ deviates from θ because of sampling error ϵ_k and an additional error term ζ_k (variance τ^2) related to the variability of individual groups around their true effect sizes. This regression uses maximally 26 estimates of effect size (two for each of the 13 groups). We analyzed only SNPs where there were GWAS summary statistics for at least 10 of the 13 groups.

The variable τ^2 from the meta-regression estimates the variance of distribution of true SNP effect sizes after accounting for the fixed covariate (phenotype). We also performed a separate random effects meta-analyses of the BD and MDD GWAS summary statistics, obtaining two estimates of τ^2, one for BD and one for MDD, to evaluate which phenotype appeared to have more heterogeneity in SNP effect sizes.

C. Comparison between the BDvsMDD and BD predictors with equal sample sizes

Since the BD GWAS has a larger sample size than the BDvsMDD GWAS, due to the fact that control individuals (included in the former) outnumber MDD individuals (included in the latter), we also calculated scores based on a subsampled version of the former, whereby the number of controls included in the BD GWAS is downsampled to the same number as that of MDD cases in the BDvsMDD GWAS, to provide a fair comparison between the two.

Our comparison of BD and BDvsMDD with similar sample sizes is shown in Supp. Figure 3A (also see Supp. Figure 6C,D). In this scenario, the performance difference is no longer significant ($p = 0.28$ for equal sample size, paired weighted t-test), meaning that the BDvsMDD predictor still does not outperform the BD predictor, even after accounting for sample size.

D. Full list of members of the Bipolar Disorder Working Group of the PGC, the Major Depressive Disorder Working Group of the PGC and the iPSYCH Consortium

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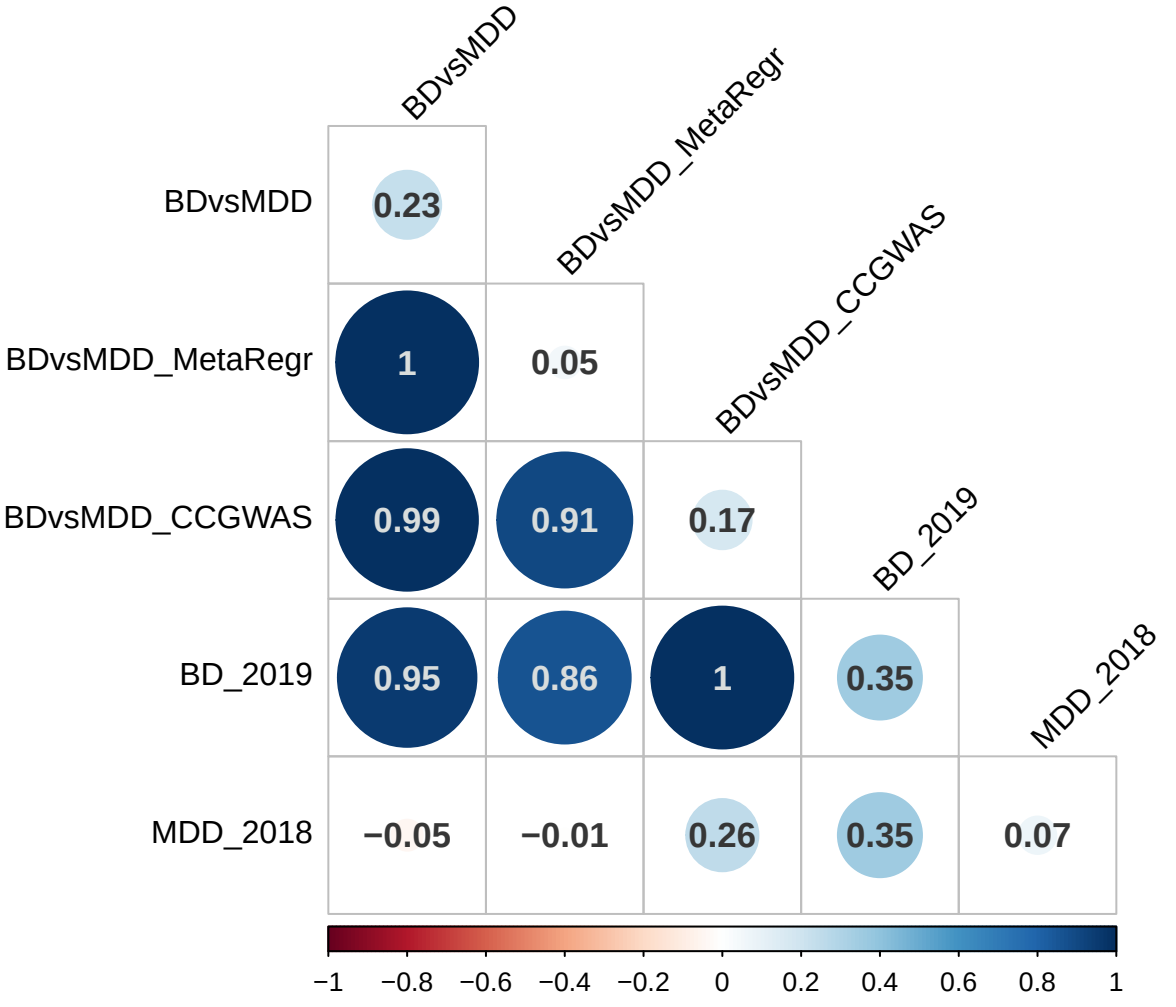
Figure 1A.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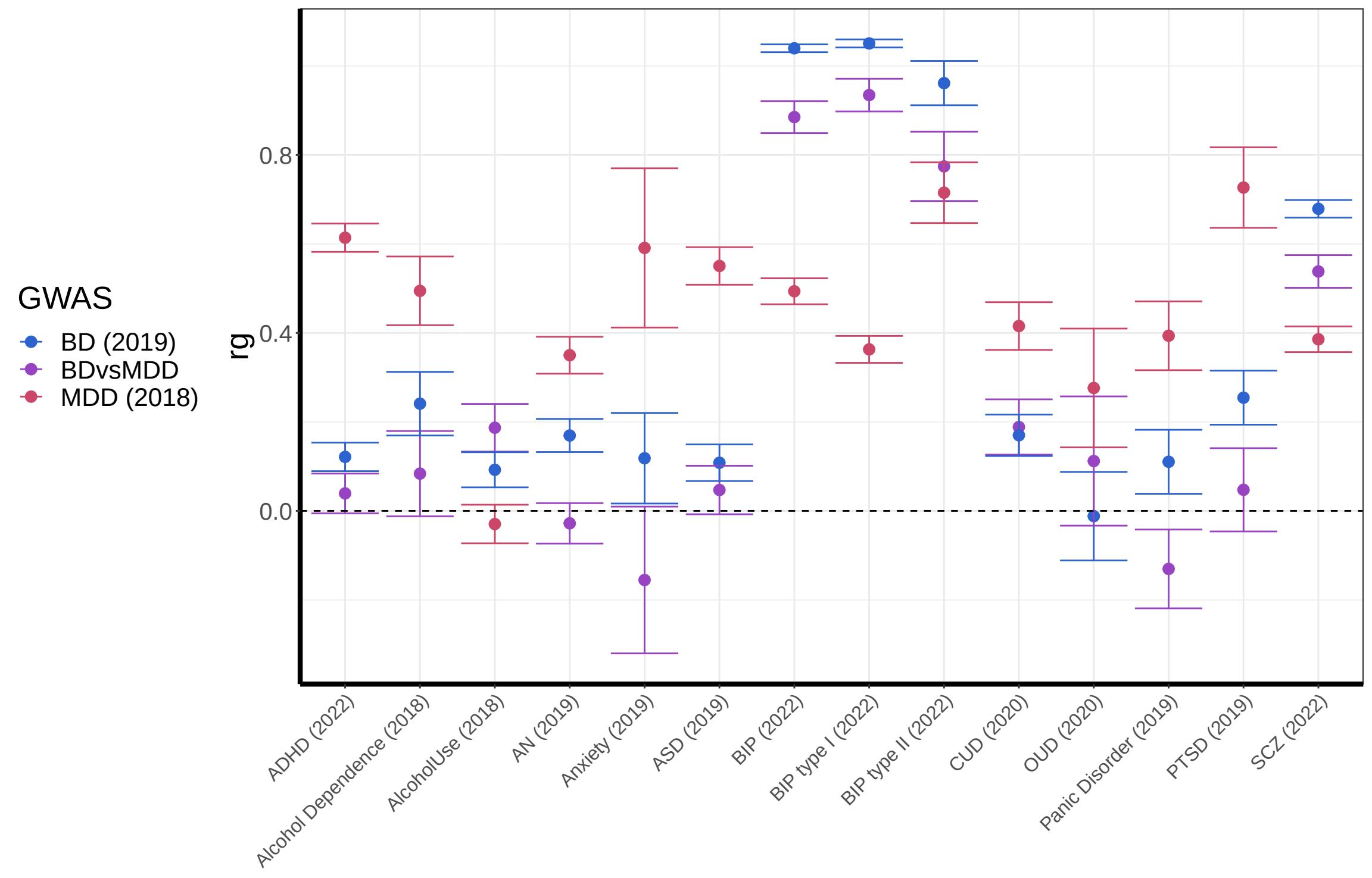
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AlcoholUse (2018)
AN (2019)
Anxiety (2019)
ASD (2019)
BIP (2022)
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BIP type II (2022)
CUD (2020)
OUD (2020)
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Figure 1B.

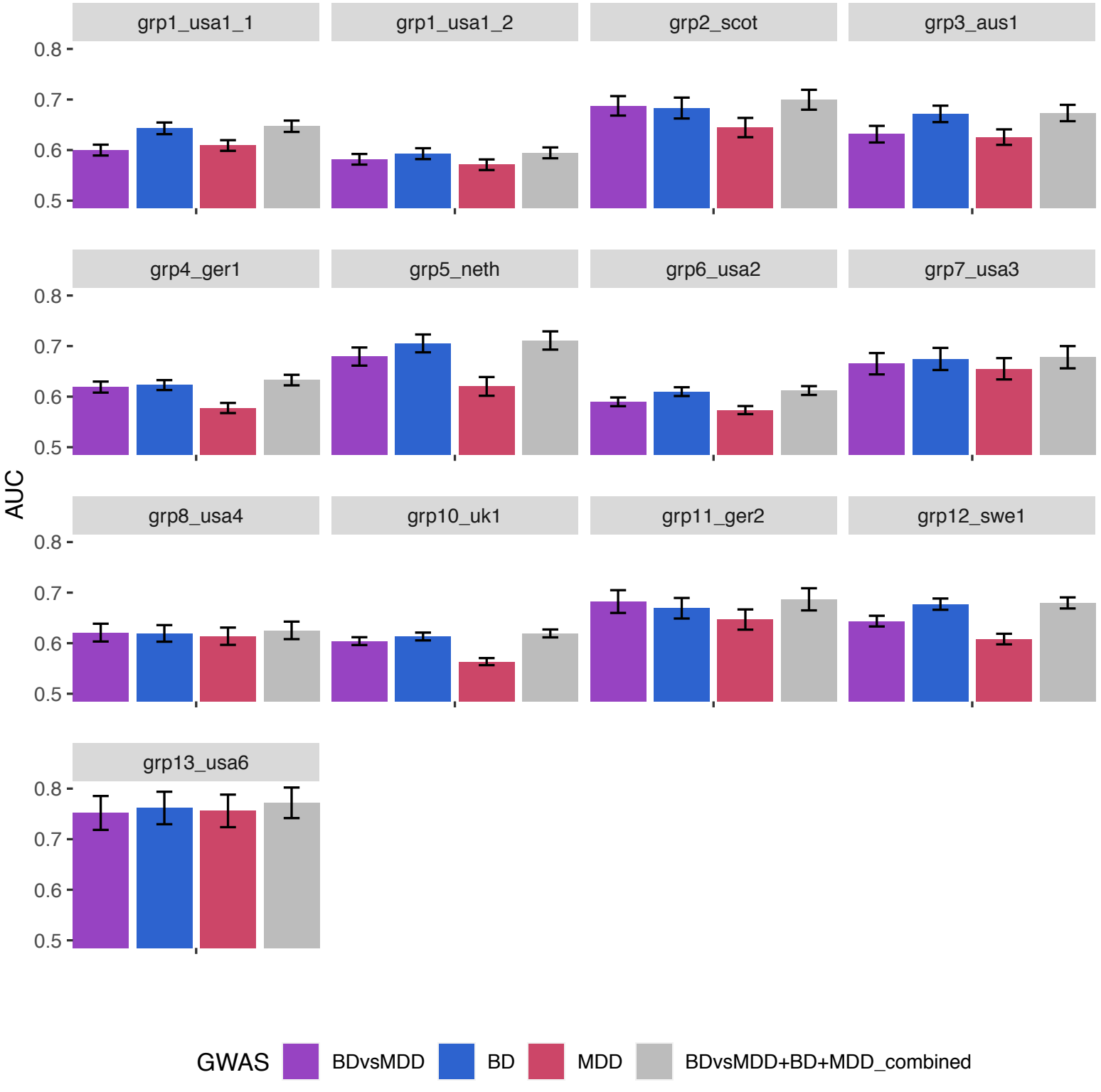


Figure 2A.

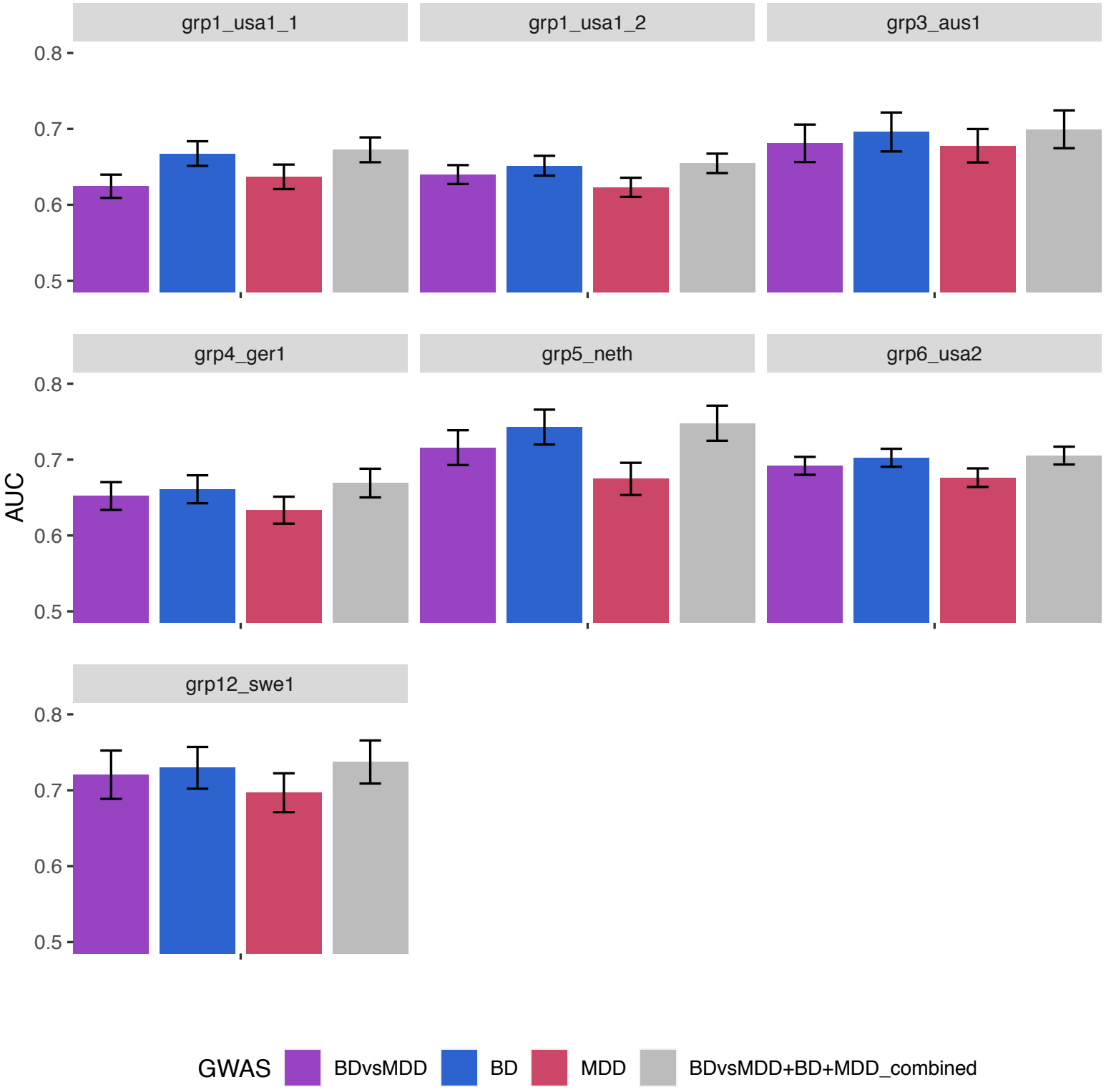
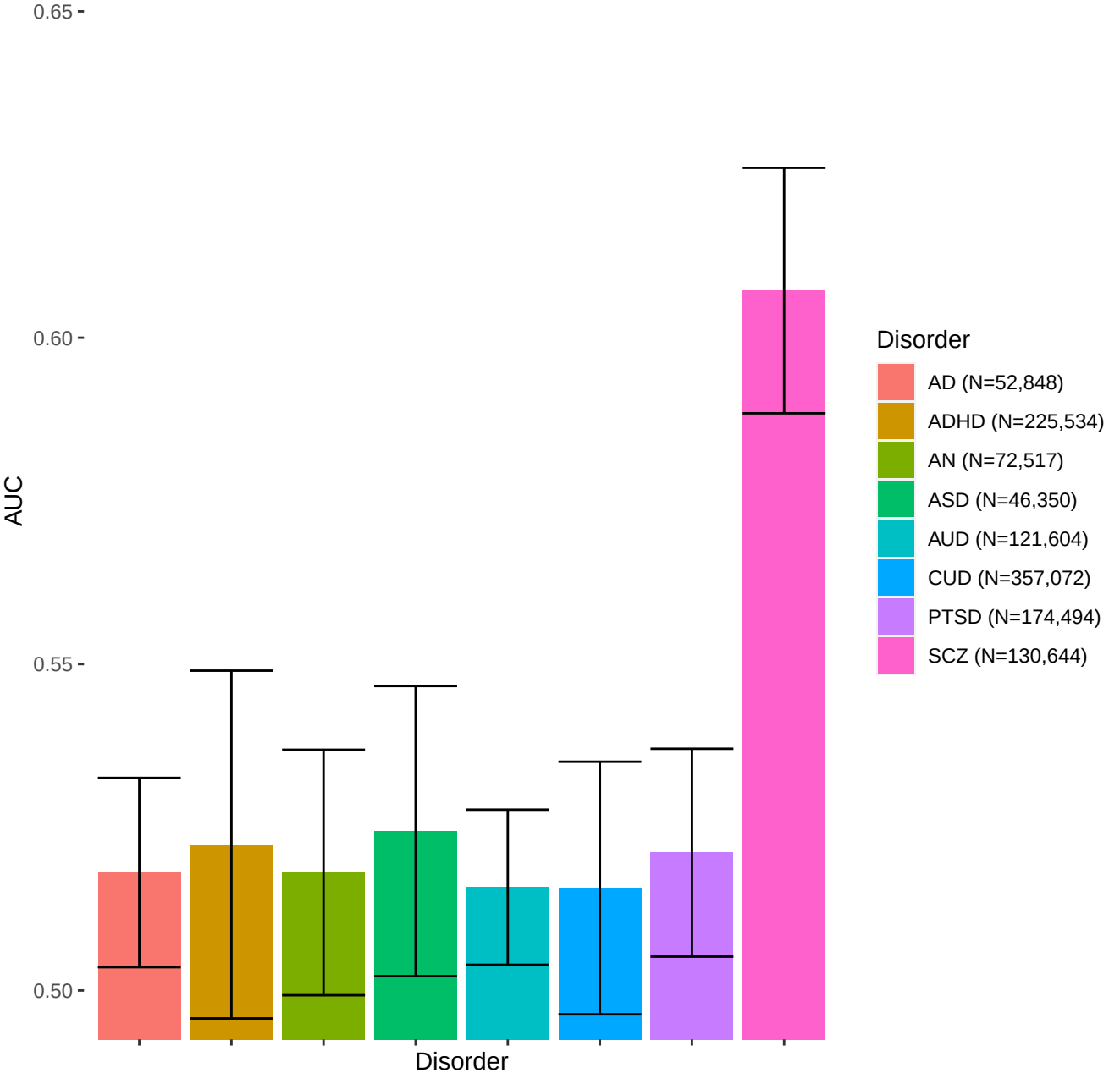


Figure 2B.

Figure 3.


0.65
0.60
0.55
0.50
AUC
Disorder
Disorder
AD (N=52,848)
ADHD (N=225,534)
AN (N=72,517)
ASD (N=46,350)
AUD (N=121,604)
CUD (N=357,072)
PTSD (N=174,494)
SCZ (N=130,644)

		Null model (predicted by 10 PCs)	Full model (predicted by BDvsMDD + 10 PCs)	Full model combined predictor (predicted by BDvsMDD + BD + MDD + 10 PCs)
BDvsMDD	**AUC**	0.563	0.578	0.587
	Nagelkerke R2	0.99%	1.39%	1.83%
	Nk R2 adjusted	-	0.40%	0.84%
ConvertBDvsMDD_0m	**AUC**	0.547	0.562	0.578
	Nagelkerke R2	0.33%	0.65%	1.02%
	Nk R2 adjusted	-	0.32%	0.69%

Note: Nagelkerke R2 adjusted = (Nagelkerke R2 Full model) - (Nagelkerke R2 Null model)

Table 1.