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Biological Psychiatry

The Genetics of the Mood Disorder Spectrum: Genome-wide Association Analyses of More Than 185,000 Cases and 439,000 Controls

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ABSTRACT

BACKGROUND: Mood disorders (including major depressive disorder and bipolar disorder) affect 10% to 20% of the population. They range from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Multiple approaches have shown considerable sharing of risk factors across mood disorders despite their diagnostic distinction.

METHODS: To clarify the shared molecular genetic basis of major depressive disorder and bipolar disorder and to highlight disorder-specific associations, we meta-analyzed data from the latest Psychiatric Genomics Consortium genome-wide association studies of major depression (including data from 23andMe) and bipolar disorder, and an additional major depressive disorder cohort from UK Biobank (total: 185,285 cases, 439,741 controls; nonoverlapping $N = 609,424$).

RESULTS: Seventy-three loci reached genome-wide significance in the meta-analysis, including 15 that are novel for mood disorders. More loci from the Psychiatric Genomics Consortium analysis of major depression than from that for bipolar disorder reached genome-wide significance. Genetic correlations revealed that type 2 bipolar disorder correlates strongly with recurrent and single-episode major depressive disorder. Systems biology analyses highlight both similarities and differences between the mood disorders, particularly in the mouse brain cell types implicated by the expression patterns of associated genes. The mood disorders also differ in their genetic correlation with educational attainment—the relationship is positive in bipolar disorder but negative in major depressive disorder.

CONCLUSIONS: The mood disorders share several genetic associations, and genetic studies of major depressive disorder and bipolar disorder can be combined effectively to enable the discovery of variants not identified by studying either disorder alone. However, we demonstrate several differences between these disorders. Analyzing subtypes of major depressive disorder and bipolar disorder provides evidence for a genetic mood disorders spectrum.

Keywords: Affective disorders, Bipolar disorder, Genetic correlation, Genome-wide association study, Major depressive disorder, Mood disorders

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Mood disorders affect 10% to 20% of the global population across their lifetime, ranging from brief episodes to incapacitating conditions that markedly impact lives (1–4). Major depressive disorder and bipolar disorder are the most common forms of mood disorder, and they have been grouped together since the publication of the DSM-III in 1980 (5). Although both disorders are given dedicated chapters in the DSM-5, they remain grouped as mood disorders in the ICD-11 (6,7).

Depressive episodes are common to major depressive disorder and type 2 bipolar disorder, and they are usually present in type 1 bipolar disorder (7). The bipolar disorders are distinguished from major depressive disorder by the presence of mania in type 1 bipolar disorder and hypomania in type 2 bipolar disorder (7). However, these distinctions are not absolute—some individuals with major depressive disorder develop bipolar disorder, and some endorse manic or hypomanic symptoms (8–10). Following a first depressive episode, a nonremitting individual might develop bipolar disorder or recurrent major depressive disorder. Treatment guidelines for these disorders differ (11,12). Identifying shared and distinct genetic associations for major depressive disorder and bipolar disorder could aid our understanding of these diagnostic trajectories.

Twin studies suggest that 35% to 45% of variance in risk for major depressive disorder, and 65% to 70% for bipolar disorder, is accounted for by additive genetic factors (13). These genetic components are partially shared, with a twin genetic correlation (r_g) of approximately 65% and a common variant–based r_g of 30% to 35% derived from genome-wide association study (GWAS) results (14–17). Progress has been made in identifying specific genetic variants that underlie genetic risk. Recently, the Psychiatric Genomics Consortium (PGC) published the results

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of a GWAS of bipolar disorder that included more than 20,000 cases, with 30 genomic loci reaching genome-wide significance (16). They also performed a GWAS of major depression that included more than 135,000 individuals with major depressive disorder and other definitions of depression, and found 44 loci reaching genome-wide significance (15). The PGC GWAS of major depression has since been combined with a broad depression GWAS (see Supplemental Note in Supplement 1).

GWASs have identified statistical associations of genetic loci with major depressive disorder and with bipolar disorder individually, but no GWAS has explored the genetic relationship between these disorders. In addition, both disorders exhibit considerable clinical heterogeneity and can be separated into subtypes. For example, the DSM-5 includes categories for type 1 and type 2 bipolar disorder, and for single-episode and recurrent major depressive disorder (7). We used the PGC analyses of major depression and bipolar disorder, along with analyses of formally defined major depressive disorder from the UK Biobank, to explore 2 aims (18,19). First, we sought to identify shared and distinct mood disorder genetics by combining studies of major depressive disorder and bipolar disorder. We then explored the genetic relationship of mood disorders to traits from the wider GWAS literature. Second, we assessed genetic similarities and differences between subtypes of bipolar disorder (from the PGC) and major depressive disorder (from the UK Biobank) through comparison of genetic correlations and polygenic risk scores.

METHODS AND MATERIALS

Participants

Our primary aim was to combine analyses of bipolar disorder and major depression to examine the shared and distinct genetics of these disorders. Full descriptions of each study and its composite cohorts are provided in previous articles (15,16,19). Brief descriptions are provided in Supplement 1. Summary statistics were derived from participants of Western European ancestries, and unless otherwise specified are available at https://www.med.unc.edu/pgc/results-and-downloads.

Major depression data were drawn from the full cohort reported by Wray *et al.* (PGC MDD) (135,458 cases, 344,901 controls) (15). These included data from 23andMe (20), access to which requires a data transfer agreement; consequently, the data analyzed here differ from the publicly available summary statistics. Data for bipolar disorder were drawn from the discovery analysis previously reported (PGC BD) (20,352 cases, 31,358 controls), not including replication results (16).

Second, we wished to examine genetic correlations between mood disorder subtypes. Summary statistics were available for the primary bipolar disorder subtypes, type 1 bipolar disorder (BD1) (14,879 cases, 30,992 controls) and type 2 bipolar disorder (BD2) (3421 cases, 22,155 controls), and for schizoaffective bipolar disorder (SAB) (977 cases, 8690 controls), a mood disorder that includes psychotic symptoms. Controls were shared across these subtype analyses.

Subtype GWASs were not available from PGC MDD. Instead, a major depressive disorder cohort was derived from the online mental health questionnaire in the UK Biobank (UKB MDD) (29,475 cases, 63,482 controls) (resource 22 on http://biobank.ctsu.ox.ac.uk) (18). The definition of major depressive disorder in this cohort is based on that in the DSM-5, as described in full elsewhere (18) and in Table S1 in Supplement 2 (7). Individuals meeting criteria for major depressive disorder were classified with recurrent major depressive disorder if they reported multiple depressed periods across their lifetime (rMDD) (N = 17,451 cases) and single-episode major depressive disorder otherwise (sMDD) (N = 12,024 cases) (Table S1 in Supplement 2). Individuals reporting symptoms of depression but not meeting case criteria were excluded from the UKB MDD cohort but were used as a "subthreshold depression" subtype (subMDD) to examine the continuity of genetic associations with major depressive disorder below clinical thresholds (N = 21,596 cases). All subtypes were analyzed with all controls. Details on the quality control and analysis of the UK Biobank phenotypes are provided in Supplement 1.

Meta-analysis of GWAS Data

We meta-analyzed PGC MDD and UKB MDD cohorts to obtain a single major depressive disorder GWAS (combined MDD cohort). We meta-analyzed the combined MDD cohort with PGC BD, comparing mood disorder cases with controls (MOOD). Further meta-analyses were performed between the PGC MDD cohort and each mood disorder subtype to assess the relative increase in variant discovery when adding different mood disorder definitions to the PGC MDD study (Supplemental Methods in Supplement 1).

Summary statistics were limited to common variants (minor allele frequency $>$ 0.05) (Supplemental Methods in Supplement 1) genotyped or imputed with high confidence (INFO score $>$ 0.6) in all studies. Controls were shared between PGC MDD and PGC BD studies, and (because the PGC MDD study included summary data) the extent of this overlap was unknown. Meta-analyses were therefore performed in METACARPA, which controls for sample overlap of unknown extent between studies using the variance–covariance matrix of the observed effect sizes at each variant, weighted by the sample sizes (21,22). METACARPA adjusted adequately for known overlap between cohorts (Supplemental Methods in Supplement 1). For later analyses (particularly linkage disequilibrium score regression [LDSC]), we used as the sample size a "nonoverlapping N" estimated for each meta-analysis (Supplemental Methods in Supplement 1). The definition, annotation, and visualization of each meta-analysis are described in Supplemental Methods in Supplement 1.

Sensitivity Analysis Using Downsampled PGC MDD Data

Cross-trait meta-analyses may be biased if the power of the composite analyses differs substantially (23,24). The mean chi-square of the combined MDD cohort [1.7] exceeded that of PGC BD [1.39], suggesting that this bias may affect our results (Table S2 in Supplement 2). We therefore repeated our analyses, meta-analyzing UKB MDD with summary statistics for PGC MDD that did not include participants from 23andMe nor the UK Biobank (mean chi-square = 1.35). All analyses were performed on the full and the downsampled analyses, with the exception of generalized summary-based Mendelian randomization (GSMR) analyses. Full results of the downsampled analyses are described in Supplemental Results in Supplement 1.

Estimation of Single Nucleotide Polymorphism–Based Heritability and Genetic Correlations With Published GWASs

Single nucleotide polymorphism (SNP)–based heritability was assessed using LDSC (25). SNP-based heritability estimates were transformed to the liability scale, assuming population prevalences of 15% for the combined MDD cohort, 1% for the PGC BD cohort, and 16% for the MOOD cohort, and lower and upper bounds of these prevalences for comparison (Supplemental Methods in Supplement 1). LDSC separates genome-wide inflation into a component resulting from polygenicity and a component resulting from confounding (25). Inflation not due to polygenicity was quantified as (intercept − 1)/(mean observed χ^2 − 1) (26). Genetic correlations were calculated in LDSC between each analysis and 414 traits curated from published GWASs. Local estimates of SNP-based heritability and genetic covariance were obtained using the Heritability Estimator From Summary Statistics version 0.5.4b (Supplemental Methods and Supplemental Results in Supplement 1) (27,28).

Genetic Correlations Between Subtype Analyses

To assess the structure of genetic correlations within the mood disorders, SNP-based heritabilities and genetic correlations were calculated in LDSC between bipolar disorder subtypes (BD1, BD2, and SAB), and major depressive disorder subtypes (rMDD, sMDD, and subMDD). Putative differences between genetic correlations were identified using a z test ($p < .05$) and formally tested by applying a block jackknife with Bonferroni correction for significance ($p < .00083$) (Supplemental Methods in Supplement 1). Differences between the genetic correlations of the PGC MDD cohort and each bipolar disorder subtype, and between the PGC BD cohort and each major depressive disorder subtype, were also tested (Bonferroni correction for significance, $p < .0083$). Genetic correlations were hierarchically clustered using the gplots package in R, version 1.4.1 (29,30). Hierarchical clustering was performed using just the subtypes and including results from 6 external GWASs relevant to mood disorders (Supplemental Methods in Supplement 1) (31–35). To validate our conclusion of a genetic mood disorder spectrum, we performed principal component analysis of the genetic correlation matrix including the 6 external GWASs (Supplemental Methods and Results in Supplement 1).

Association of PGC BD Polygenic Risk Scores With MDD Subtypes

Polygenic risk score analyses were performed using PRSice2 to assess whether the rMDD cohort was genetically more similar to the PGC BD cohort than was the sMDD or subMDD cohort (Supplemental Methods in Supplement 1) (36).

Genewise, Gene-Set, and Tissue and Single-Cell Enrichment Analyses

For all analyses, the p values of SNPs in gene regions (defined as Ensembl gene locations) were combined as the aggregate of the mean and smallest p value to yield genewise p values, using MAGMA version 1.06 (Supplemental Methods and Results in Supplement 1) (37). Gene-set analysis was performed in MAGMA (Supplemental Methods and Results in Supplement 1). Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (Genotype-Tissue Expression project, version 7) and broadly defined (level 1) and narrowly defined (level 2) mouse brain cell types (38,39). Analyses were performed in MAGMA following previously described methods with minor modifications, with Bonferroni correction for significance (Supplemental Methods in Supplement 1) (38). Similar analyses can be performed in LDSC-SEG—we report MAGMA results, which reflect specificity of expression across the range, whereas LDSC-SEG compares the top 10% of the range with the remainder (40). Results using LDSC are included in Tables S9–S11 in Supplement 2.

Mendelian Randomization (GSMR)

Bidirectional Mendelian randomization analyses were performed using the GSMR option in GCTA to allow exploratory inference of the causal direction of known relationships between mood disorder traits and other traits (41,42). Specifically, we explored the relationships between the mood disorder analyses (MOOD, combined MDD, and PGC BD) and schizophrenia, intelligence, educational attainment, body mass index (BMI), and coronary artery disease (Supplemental Methods in Supplement 1) (32,43–46). These traits were previously examined in the PGC major depression GWAS—we additionally tested intelligence following the results of our genetic correlation analyses (15).

Conditional and Reversed-Effect Analyses

Additional analyses were performed to identify shared and distinct mood disorder loci, using mtCOJO, an extension of GSMR (Supplemental Methods in Supplement 1) (41,42). Analyses were performed on combined MDD conditional on PGC BD, and on PGC BD conditional on combined MDD (Supplemental Results in Supplement 1). To identify loci with opposite directions of effect between combined MDD and PGC BD, the MOOD meta-analysis was repeated with reversed direction of effects for PGC BD (Supplemental Methods and Results in Supplement 1).

RESULTS

Evidence for Confounding in Meta-analyses

Meta-analysis results were assessed for genome-wide inflation of test statistics using LDSC (25). Generally, the LDSC intercept was significantly >1 (1.00–1.06), which has previously been interpreted as confounding (Table S2 in Supplement 2). However, such inflation can occur in large cohorts without confounding (47). Estimates of inflation not due to polygenicity were small in all meta-analyses (4%–7%) (Table S2 in Supplement 2).

Combined MOOD Meta-analysis

We meta-analyzed the PGC MDD, PGC BD, and UKB MDD cohorts (MOOD cohort, cases = 185,285, controls = 439,741, nonoverlapping N = 609,424). In all, 73 loci reached genome-wide significance, of which 55 were also seen in the meta-

Table 1. Loci of Genome-wide Significance in the MOOD Meta-analysis[a]

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	*p* Value	Previous Report
1	1	37192741	rs1002656	T	C	0.97	0.005	2.71×10^{-11}	DO, N
2	1	72837239	rs7531118	T	C	0.96	0.004	1.05×10^{-16}	D, DO, S, O
4	1	80795989	rs6667297	A	G	0.97	0.005	5.86×10^{-11}	D, DO
5	1	90796053	rs4261101	A	G	0.97	0.005	1.78×10^{-8}	D
6	1	175913828	rs10913112	T	C	0.97	0.005	1.46×10^{-10}	DO, O
7	1	177370033	rs16851203	T	C	0.96	0.007	2.38×10^{-9}	DO, S, O
9	2	22582968	rs61533748	T	C	0.97	0.004	3.84×10^{-11}	DO, N
10	2	57987593	rs11682175	T	C	0.97	0.004	2.18×10^{-11}	D, DO, BS, N, S, O
11	2	157111313	rs1226412	T	C	1.03	0.005	1.27×10^{-8}	D, DO, N, O
12	2	198807015	rs1518367	A	T	0.97	0.005	1.18×10^{-8}	BS, S, O
13	3	108148557	rs1531188	T	C	0.96	0.006	1.61×10^{-9}	O
14	3	158107180	rs7430565	A	G	0.97	0.004	2.30×10^{-11}	D, DO, N, O
16	4	42047778	rs34215985	C	G	0.97	0.006	1.72×10^{-10}	D, DO, N
17	5	77709430	rs4529173	T	C	0.97	0.005	4.29×10^{-9}	O
18	5	88002653	rs447801	T	C	1.03	0.004	2.29×10^{-10}	D, DO, N, O
19	5	92995013	rs71639293	A	G	1.03	0.005	5.85×10^{-9}	DO, N
20	5	103904226	rs12658032	A	G	1.04	0.005	2.19×10^{-16}	D, DO, N, O
21	5	106603482	rs55993664	A	C	0.97	0.006	1.87×10^{-8}	Novel locus
22	5	124251883	rs116755193	T	C	0.97	0.005	1.47×10^{-10}	D, O
23	5	164523472	rs11135349	A	C	0.97	0.004	2.96×10^{-11}	D, DO, N
24	5	166992078	rs4869056	A	G	0.97	0.005	5.21×10^{-9}	D
25	6	28673998	rs145410455	A	G	0.94	0.007	7.17×10^{-18}	D, DO, BO, BS, DS, N, S, O
26	6	101339400	rs7771570	T	C	0.97	0.004	9.68×10^{-10}	DO, N, O
27	6	105365891	rs1933802	C	G	0.98	0.004	1.05×10^{-8}	DO, S, O
28	7	12267221	rs4721057	A	G	0.97	0.004	7.31×10^{-11}	D, DO, N, O
29	7	24826589	rs79879286	C	G	1.04	0.006	1.97×10^{-11}	B, BS, DO, S
30	7	82514089	rs34866621	T	C	1.03	0.005	2.21×10^{-8}	DO, O
31	7	109099919	rs58104186	A	G	1.03	0.004	7.12×10^{-9}	D, DO
34	9	11379630	rs10959753	T	C	0.96	0.005	1.45×10^{-13}	D, DO, N, O
35	9	37207269	rs4526442	T	C	0.96	0.006	7.97×10^{-11}	DO, O
36	9	81413414	rs11137850	A	G	1.03	0.005	1.25×10^{-8}	Novel locus
38	9	119733380	rs10759881	A	C	1.03	0.005	8.56×10^{-9}	D, DO
40	9	122664468	rs10818400	T	G	0.98	0.004	1.29×10^{-8}	N
41	9	126682068	rs7029033	T	C	1.04	0.008	2.61×10^{-8}	D, DO, O
42	10	104684544	rs78821730	A	G	0.96	0.007	2.95×10^{-8}	N, BS, S, O
43	10	106563924	rs61867293	T	C	0.96	0.005	5.64×10^{-12}	D, DO, N, O
44	11	16293680	rs977509	T	C	0.97	0.005	1.19×10^{-8}	DO, N, O
45	11	31850105	rs1806153	T	G	1.03	0.005	2.81×10^{-9}	D, DO, N, O
46	11	32765866	rs143864773	T	C	1.04	0.008	1.70×10^{-8}	Novel locus
47	11	61557803	rs102275	T	C	0.97	0.005	5.04×10^{-11}	B, DO, BO, O
48	11	63632673	rs10792422	T	G	0.98	0.004	2.18×10^{-8}	O
49	11	88743208	rs4753209	A	T	0.97	0.004	4.15×10^{-9}	DO, N, O
50	11	99268617	rs1504721	A	C	0.98	0.004	2.24×10^{-8}	O
51	11	113392994	rs2514218	T	C	0.97	0.005	3.22×10^{-10}	DO, BS, N, S, O
52	12	2344644	rs769087	A	G	1.03	0.005	3.27×10^{-8}	B, BD, BO, DS, BS, S, O
53	12	23947737	rs4074723	A	C	0.97	0.004	3.18×10^{-9}	D, DO, N, O
54	12	121186246	rs58235352	A	G	0.95	0.009	1.64×10^{-10}	DO, O
55	12	121907336	rs7962128	A	G	1.02	0.004	3.63×10^{-8}	Novel locus
56	13	44327799	rs4143229	A	C	0.95	0.008	2.73×10^{-10}	D
57	13	53625781	rs12552	A	G	1.04	0.004	1.25×10^{-23}	D, DO, O
58	14	42074726	rs61990288	A	G	0.97	0.004	2.29×10^{-10}	D, DO, O
60	14	64686207	rs915057	A	G	0.98	0.004	1.92×10^{-8}	D, DO, O
61	14	75130235	rs1045430	T	G	0.97	0.004	9.83×10^{-11}	D, DO, N, O

Table 1. Continued

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	*p* Value	Previous Report
62	14	104017953	rs10149470	A	G	0.97	0.004	1.15×10^{-10}	D, DS, DO, BS, S, O
63	15	36355868	rs1828385	A	C	0.97	0.004	1.15×10^{-8}	Novel locus
64	15	37643831	rs8037355	T	C	0.97	0.004	4.09×10^{-15}	D, DO, O
65	16	6310645	rs8063603	A	G	0.97	0.005	5.36×10^{-11}	D, DO
66	16	7667332	rs11077206	C	G	1.03	0.004	5.49×10^{-10}	D, DO, N, O
67	16	13038723	rs12935276	T	G	0.97	0.005	4.75×10^{-10}	D, DO, N, O
68	16	13750257	rs7403810	T	G	1.03	0.005	7.52×10^{-11}	DO, BS, S, O
69	16	72214276	rs11643192	A	C	1.03	0.004	1.46×10^{-11}	D, O
70	17	27363750	rs75581564	A	G	1.04	0.006	2.47×10^{-10}	D, DO, O
71	18	31349072	rs4534926	C	G	1.03	0.004	9.14×10^{-9}	DO, N
72	18	36883737	rs62099069	A	T	0.97	0.004	9.52×10^{-10}	D, O
73	18	42260348	rs117763335	T	C	0.97	0.005	1.33×10^{-8}	O
74	18	50614732	rs11663393	A	G	1.03	0.004	1.56×10^{-10}	D, DO, N, O
75	18	52517906	rs1833288	A	G	1.03	0.005	4.54×10^{-8}	D, DS, DO, N, S, O
76	18	53101598	rs12958048	A	G	1.04	0.005	4.86×10^{-14}	D, DO, BS, N, S, O
77	19	30939989	rs33431	T	C	1.02	0.004	4.04×10^{-8}	DO, O
78	20	45841052	rs910187	A	G	0.97	0.005	3.09×10^{-9}	DO, O
79	22	41621714	rs2179744	A	G	1.03	0.005	3.83×10^{-12}	D, B, DO, BS, N, S, O
80	22	42815358	rs7288411	A	G	1.03	0.005	3.86×10^{-8}	Novel locus
81	22	50679436	rs113872034	A	G	0.96	0.006	1.10×10^{-9}	O

A1, effect allele; A2, noneffect allele; B, locus previously implicated in Psychiatric Genomics Consortium bipolar disorder study; BD, locus previously implicated in previous combined studies of bipolar disorder and major depressive disorder; BO, locus previously implicated in other studies of bipolar disorder; BP, base position; BS, locus implicated in previous combined studies of bipolar disorder and schizophrenia; Chr, chromosome; D, locus previously implicated in Psychiatric Genomics Consortium major depressive disorder study; DO, locus previously implicated in other studies of major depressive disorder or depressive symptoms; DS, locus implicated in previous combined studies of major depressive disorder and schizophrenia; Locus, shared locus number for annotation (Table S3 in Supplement 2); MOOD, combined major depressive disorder cohorts with Psychiatric Genomics Consortium bipolar disorder cohort; N, locus previously implicated in studies of neuroticism; O, locus previously implicated in other studies (see Table S4 in Supplement 2); OR, odds ratio; S, locus previously implicated in studies of schizophrenia; SE, standard error; SNP, single nucleotide polymorphism.

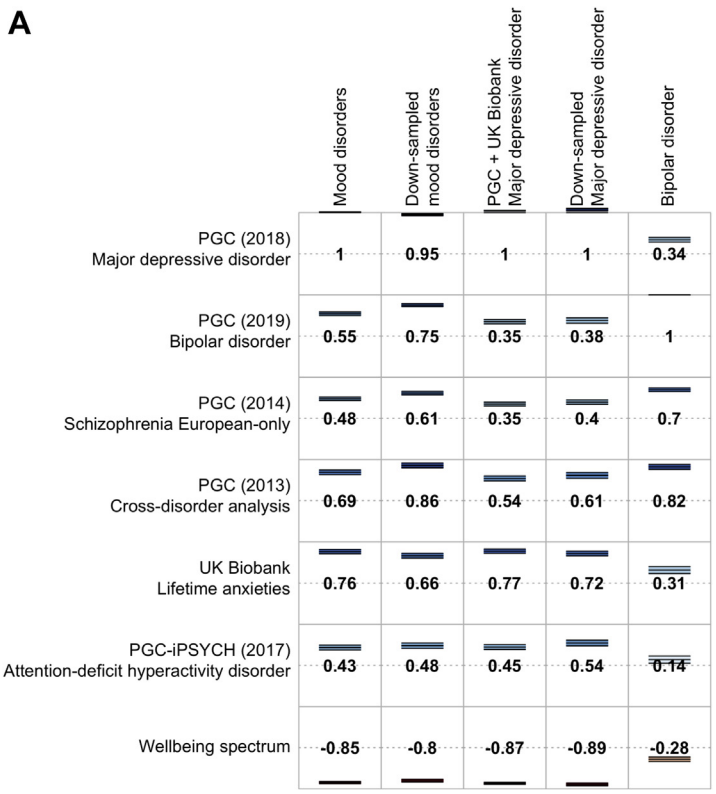
[a]Genome-wide significance $p < 5 \times 10^{-8}$.

analysis of PGC MDD and UKB MDD (combined MDD cohort) (Table 1, Table S3 in Supplement 2, and Figures S1–S8 in Supplement 1). Of the 44 PGC MDD loci, 39 reached genome-wide significance in the MOOD analysis. In comparison, only 4 of the 19 PGC BD loci reached genome-wide significance in the MOOD analysis (Table S3 in Supplement 2). MOOD loci overlapped considerably with those found in previous studies of depression and depressive symptoms (51 of 73 loci) (20,23,48–52), bipolar disorder (3 of 73 loci) (53–56), neuroticism (32 of 73 loci) (23,57–59), and schizophrenia (15 of 73 loci) (32,60), although there is overlap between the participants in the MOOD cohort and participants in many of these studies. Locus 52 (chromosome 12) passed genome-wide significance in a previous meta-analysis of broad depression and bipolar disorder, although the 2 other loci from this study did not replicate (51). Of the 73 associations, 6 loci are entirely novel ($p > 5 \times 10^{-8}$ in previous studies of all phenotypes) (Table 1; Table S4 in Supplement 2).

Downsampled MOOD data (cases = 95,481, controls = 287,932, nonoverlapping N = 280,214) showed increased similarity to PGC BD data compared with MOOD data but remained more similar to PGC MDD data. Nineteen loci reached genome-wide significance in the analysis of downsampled MOOD data, including 9 (20%) from the PGC MDD analysis, compared with 2 (11%) reported in the PGC BD findings (Table S3 in Supplement 2). Of 19 loci, 17 were also observed in the MOOD analysis. Of the 2 loci not observed in the MOOD study, 1 passed genome-wide significance in the PGC BD study.

SNP-Based Heritability and Genetic Correlations

The estimate of SNP-based heritability for the MOOD cohort (8.8%) was closer to that for the PGC MDD cohort (8.8%) than for the PGC BD cohort (20%). Significant genetic correlations between the MOOD cohort and other traits included psychiatric and behavioral, reproductive, cardiometabolic, and sociodemographic traits (Figure 1 and Table S5 in Supplement 2). Genetic correlations with psychiatric and behavioral traits are consistently observed across psychiatric traits (17,61). The genetic correlation between the MOOD cohort and educational attainment was −0.06 (p = .004), intermediate between the results of the combined MDD analysis (r_g = −.11) and those of the PGC BD analysis (r_g = .19) (Table S6 in Supplement 2). Notably, the genetic correlation with intelligence was not significant in any of the 3 analyses ($p > 1.27 \times 10^{-4}$). However, sensitivity analyses (see below) indicated that including 23andMe data in the PGC MDD analysis obscured a negative genetic correlation with intelligence.



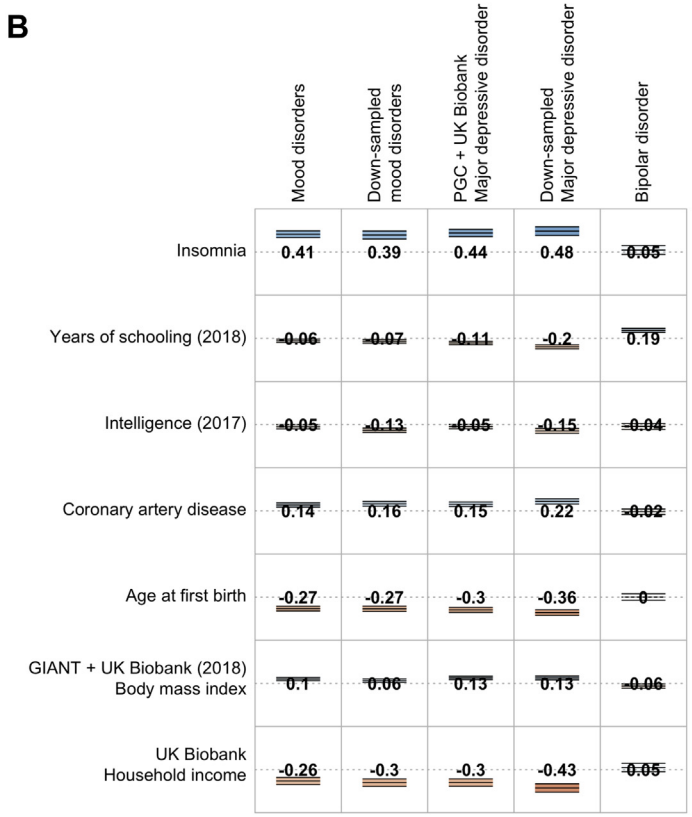


Figure 1. Selected genetic correlations of **(A)** psychiatric traits and **(B)** other traits with the main meta-analysis (MOOD cohort), the separate mood disorder analyses (combined major depressive disorder cohorts and Psychiatric Genomics Consortium [PGC] bipolar disorder cohort), and the downsampled analyses (downsampled MOOD cohort, downsampled major depressive disorder cohort). Full genetic correlation results are provided in Table S5 in Supplement 2. GIANT, The Genetic Investigation of Anthropometric Traits consortium; iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research.

The SNP-based heritability of downsampled MOOD data from LDSC was 11%, closer to PGC MDD results than to PGC BD results (Table S2 in Supplement 2). Genetic correlations varied (Tables S5 and S7 in Supplement 2), with some more similar to those of the PGC BD cohort (schizophrenia: downsampled r_g = .61, combined MDD r_g = .35, PGC BD r_g = .7) and others more similar to those of the combined MDD cohort (attention-deficit/hyperactivity disorder: downsampled r_g = .48, combined MDD r_g = .45, PGC BD r_g = .14). The genetic correlation with intelligence was significant (r_g = −.13, $p = 5 \times 10^{-7}$), because the excluded 23andMe depression cohort has a positive genetic correlation with intelligence (r_g = .06, p = .01). The greater genetic correlation of the MOOD cohort with the combined MDD cohort (r_g = .98) compared with the PGC BD cohort (r_g = .55) persisted when we compared the downsampled MOOD cohort with the combined MDD cohort (r_g = .85) and the PGC BD cohort (r_g = .75) (Table S6 in Supplement 2).

Relationship Between Mood Disorder Subtypes

Analyses were performed using GWAS data from subtypes of bipolar disorder (BD1, BD2, and SAB) and major depressive disorder (rMDD, sMDD, and subMDD). SNP-based heritability for the subtypes were 8% for subMDD and sMDD, 10% for BD2, 12% for rMDD, 22% for BD1, and 29% for SAB (Figure 2 and Table S2 in Supplement 2).

The major depressive disorder subtypes were strongly and significantly genetically correlated (r_g = .9–.94, $p_{rg=0} <$ .00083). These correlations did not differ significantly from 1 (all $p_{rg=1} > .3$), nor from each other (all $p_{\Delta rg=0} > .5$) (Figure 2 and Table S8 in Supplement 2). BD1 and SAB were strongly correlated (r_g = .77, $p_{rg=0} = 6 \times 10^{-13}$, $p_{rg=1}$ = .03), as were BD1 and BD2 (r_g = .86, $p_{rg=0} = 3 \times 10^{-16}$, $p_{rg=1}$ = .2). However, BD2 was not significantly correlated with SAB (r_g = .22, $p_{rg=0}$ = .02).

In hierarchical clustering, BD2 clustered with the major depressive disorder subtypes rather than the bipolar disorder subtypes. The strength of correlation between BD2 and BD1 did not differ from that between BD2 and rMDD (r_g = .68, $p_{rg=0} = 3 \times 10^{-8}$, $p_{rg=1}$ = .01), following multiple testing correction (Δr_g = .18, p = .02). Overall, these results suggest that a spectrum of genetic relationships exist between major depressive disorder and bipolar disorder, with type 2 bipolar disorder bridging the two disorders (Figure 3 and Figure S9 in Supplement 1). This spectrum remained when 6 external phenotypes were added, and it was supported by results from principal component analysis (Supplemental Results and Figure S10 in Supplement 1).

Polygenic risk score analyses showed that individuals with high polygenic risk scores for bipolar disorder were more likely to report recurrent major depressive disorder than single-episode major depressive disorder, and more likely to report single-episode major depressive disorder than subthreshold depression (Supplemental Results in Supplement 1).

Tissue and Cell-Type Specificity Analyses

The results of genewise and gene-set analyses are described in Supplemental Results in Supplement 1. The tissue specificity of associated genes differed minimally between the analyses (Table S9 in Supplement 2). All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in the combined MDD and PGC BD cohorts ($p <$ .000943, Bonferroni correction for 53 regions) (Table S9 in Supplement 2). Results from downsampled MOOD and downsampled MDD analyses were generally consistent with those of the main analyses, except spinal cord was not enriched in either, nor was the cordate enriched in the downsampled MDD analysis.

In contrast, cell type enrichments differed between the combined MDD and PGC BD cohorts (Figure 4 and Tables S10

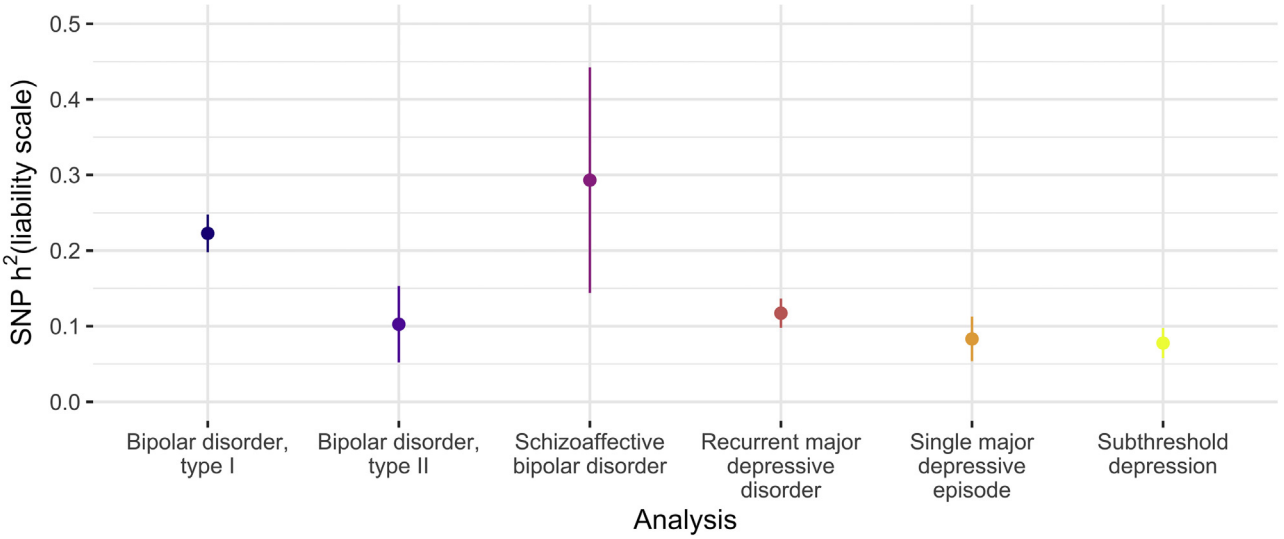


Figure 2. Single nucleotide polymorphism (SNP)–based heritability estimates for the subtypes of bipolar disorder and subtypes of major depressive disorder. Points represent SNP-based heritability estimates. Lines represent 95% confidence intervals. Full SNP-based heritability results are provided in Table S2 in Supplement 2.

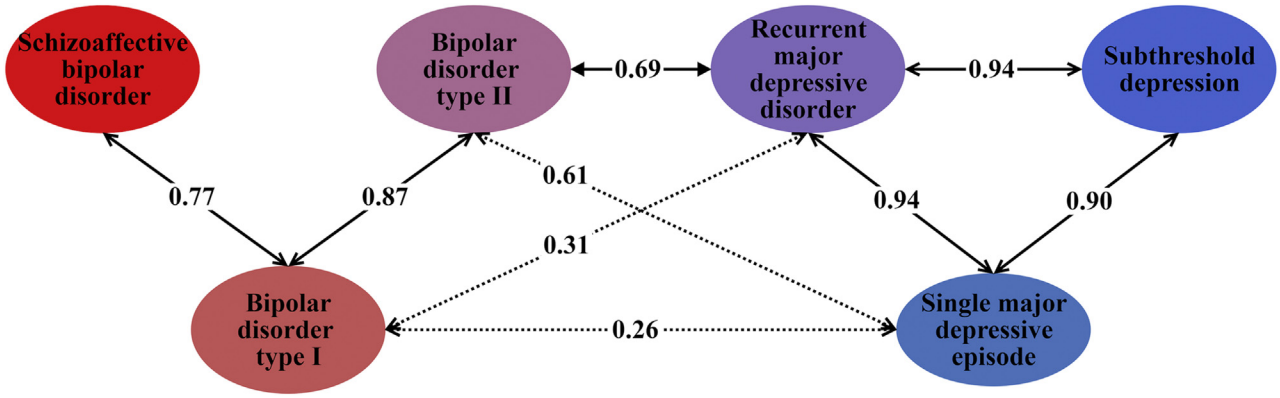


Figure 3. Genetic correlations across the mood disorder spectrum. Labeled arrows show genetic correlations that are significantly different from 0. Solid arrows represent genetic correlations that are not significantly different from 1 ($p < .00333$, Bonferroni correction for 15 tests). Full results are provided in Table S8 in Supplement 2.

and S11 in Supplement 2). Genes associated in the PGC BD cohort were enriched for expression in pyramidal cells from the CA1 region of the hippocampus and the somatosensory cortex and in striatal interneurons. None of these enrichments was significant in the combined MDD analysis. Genes associated only in the combined MDD cohort were significantly enriched for expression in neuroblasts and dopaminergic neurons from adult mice. Additional cell types (dopaminergic neuroblasts; dopaminergic, gamma-aminobutyric acidergic, and midbrain nucleus neurons from embryonic mice; interneurons; and medium spiny neurons) were enriched in both combined MDD and PGC BD cohorts, but the rank and strength of enrichment differed, most notably for medium spiny neurons. The general pattern of differences persisted when comparing the PGC BD analysis with the downsampled MDD analysis, although genes associated in the downsampled MDD cohort were not enriched for expression in adult dopaminergic neurons, embryonic midbrain nucleus neurons, interneurons, or medium spiny neurons (Figure S11 in Supplement 1).

Shared and Distinct Relationships With Mood Disorders and Inferred Causality

Bidirectional Mendelian randomization was used to investigate previously described relationships between mood disorder phenotypes (combined MDD cohort and PGC BD cohort) and external traits: schizophrenia, educational attainment, intelligence, BMI, and CAD (Figure 5 and Table S12 in Supplement 2). Associations with the PGC BD cohort should be interpreted cautiously, as only 19 loci reached genome-wide significance, several of which were removed as potentially pleiotropic in the analyses below.

Positive bidirectional relationships were observed between combined MDD, PGC BD, and schizophrenia. This finding is consistent with psychiatric disorders causing further psychiatric disorders or being correlated with other causal risk factors, including (but not limited to) a shared genetic basis.

Educational years were found to have a negative bidirectional relationship with combined MDD but a positive bidirectional relationship with PGC BD (albeit with only nominal significance from PGC BD to educational years). In contrast, no significant relationship was observed between mood phenotypes and intelligence. This finding is consistent with differing causal roles of education (or its correlates) on the mood disorders, with a weaker reciprocal effect of the mood disorders altering the length of education.

A positive association was seen between BMI and the combined MDD cohort but not from the combined MDD cohort to BMI. In contrast, only a nominally significant negative relationship was seen from the PGC BD cohort to BMI. A positive association was observed from the combined MDD cohort to CAD; no relationship was observed between CAD and the PGC BD cohort.

DISCUSSION

We identified 73 genetic loci by meta-analyzing cohorts of major depressive disorder and bipolar disorder, including 15 loci novel to mood disorders. Our mood disorders meta-analysis results (MOOD cohort) are more like our major depressive disorder analysis (combined MDD cohort) than like our bipolar disorder analysis (PGC BD cohort). Partly, this finding results from the greater power of the major depressive disorder analysis compared with that of the bipolar disorder analysis. Nevertheless, genetic associations from our sensitivity analysis with equivalently powered cohorts (using downsampled MDD instead of combined MDD data) still showed a greater similarity to associations from major depressive disorder rather than bipolar disorder.

This finding may reflect a complex genetic architecture in bipolar disorder, wherein one set of variants may be associated more with manic symptoms and another set with depressive symptoms. Variants associated more with mania may have higher effect sizes, detectable at current bipolar disorder GWAS sample sizes, and may not be strongly associated with major depressive disorder. These differences could contribute to the higher heritability of bipolar disorder compared with major depressive disorder and would be consistent with reports that most of the genetic variance for mania is not shared with depression (13,14). Meta-analysis of

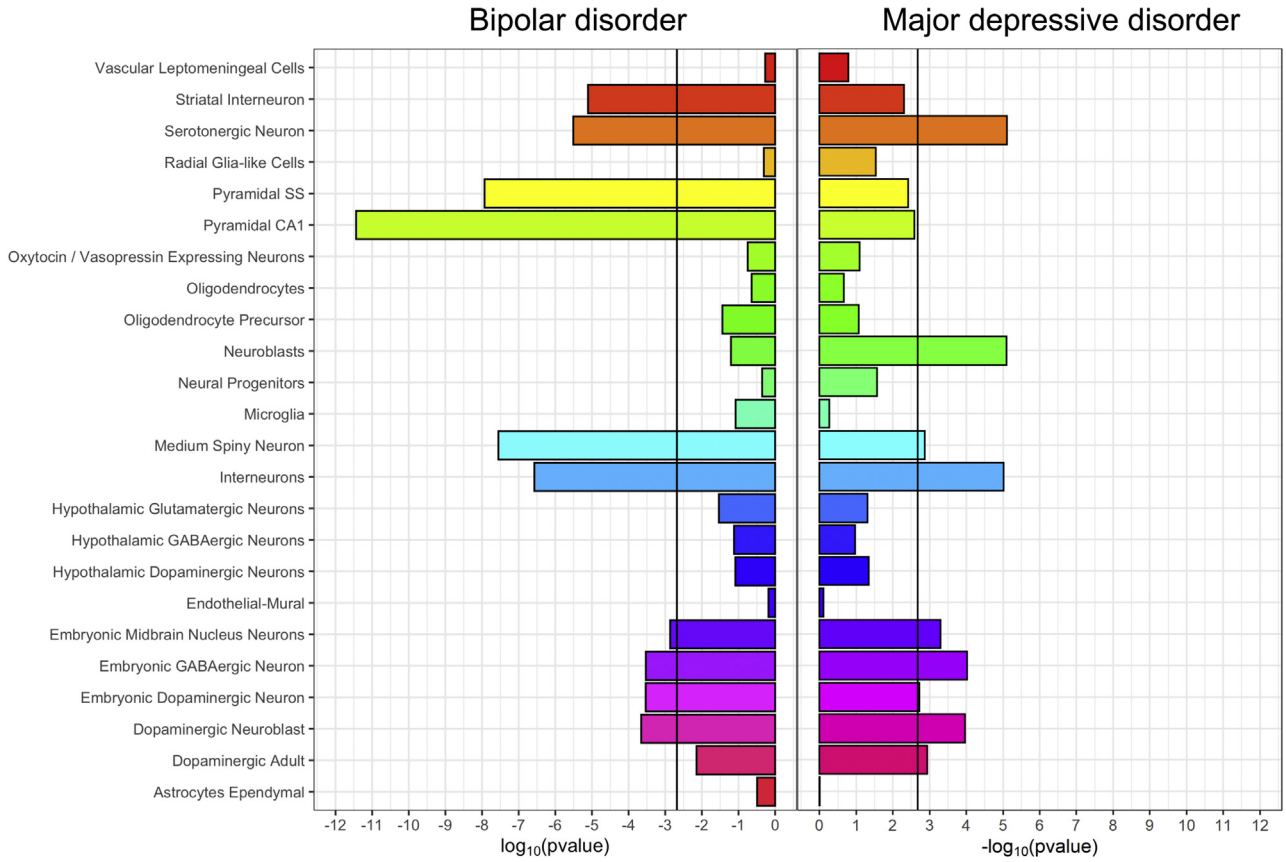


Figure 4. Cell-type expression specificity of genes associated with bipolar disorder (Psychiatric Genomics Consortium bipolar disorder study, left panel) and major depressive disorder (combined major depressive disorder studies, right panel). Black vertical lines represent significant enrichment ($p < .002$, Bonferroni correction for 24 cell types). See Table S10 in Supplement 2 for full results. GABAergic, gamma-aminobutyric acidergic; SS, somatosensory cortex.

bipolar disorder and major depressive disorder cohorts would support variants associated more with depression but not those associated with mania. This is consistent with our findings, and with depressive symptoms being both the unifying feature of the mood disorders and the core feature of major depressive disorder.

We examined the genetic relationship between mood disorder subtypes, including adding relevant external traits for context (Supplemental Results in Supplement 1). Type 2 bipolar disorder showed greater genetic similarity to major depressive disorder compared with type 1 bipolar disorder, mirroring similar findings from polygenic risk scores analyses (16,56). Individuals with high polygenic risk scores for bipolar disorder were more likely to report recurrent major depressive disorder than single-episode major depressive disorder. However, the genetic correlation of bipolar disorder with recurrent major depressive disorder was not significantly greater than that with single-episode major depressive disorder. This finding might reflect the difference in power between these methods. Genetic correlations between mood disorder subtypes support a genetic mood spectrum, with the schizophrenia-like type 1 bipolar disorder and schizoaffective bipolar disorder at one pole and the depressive disorders at the other, with type 2 bipolar disorder occupying an intermediate position.

Conditional and reversed-effect analyses (Supplemental Results in Supplement 1) suggest that few of the loci we identified are disorder specific. Nonetheless, we observed some genetic differences between the mood disorders. The expression specificity of associated genes in mouse brain cell types differed between bipolar disorder and major depressive disorder. Cell types more associated with bipolar disorder (pyramidal neurons and striatal interneurons) were also enriched in analyses of schizophrenia (38). Cell types more associated in major depressive disorder (neuroblasts, adult dopaminergic neurons, embryonic gamma-aminobutyric acidergic neurons) had weaker enrichments in schizophrenia but were enriched in analyses of neuroticism (57). The higher rank of serotonergic neurons in major depressive disorder compared with that in bipolar disorder is striking given the use of drugs targeting the serotonergic system in treating depression (62). Nevertheless, cell-type enrichment analyses require cautious interpretation, especially given the use of nonhuman reference data (38,63).

We explored potential causal relationships between the mood disorders and other traits using Mendelian randomization. Interpreting these analyses is challenging, especially for complex traits, when the ascertainment of cases varies, and when few (<20) variants are used as instruments (as in the PGC BD and downsampled analyses presented) (41,64,65). Mood disorders demonstrate considerable heterogeneity,

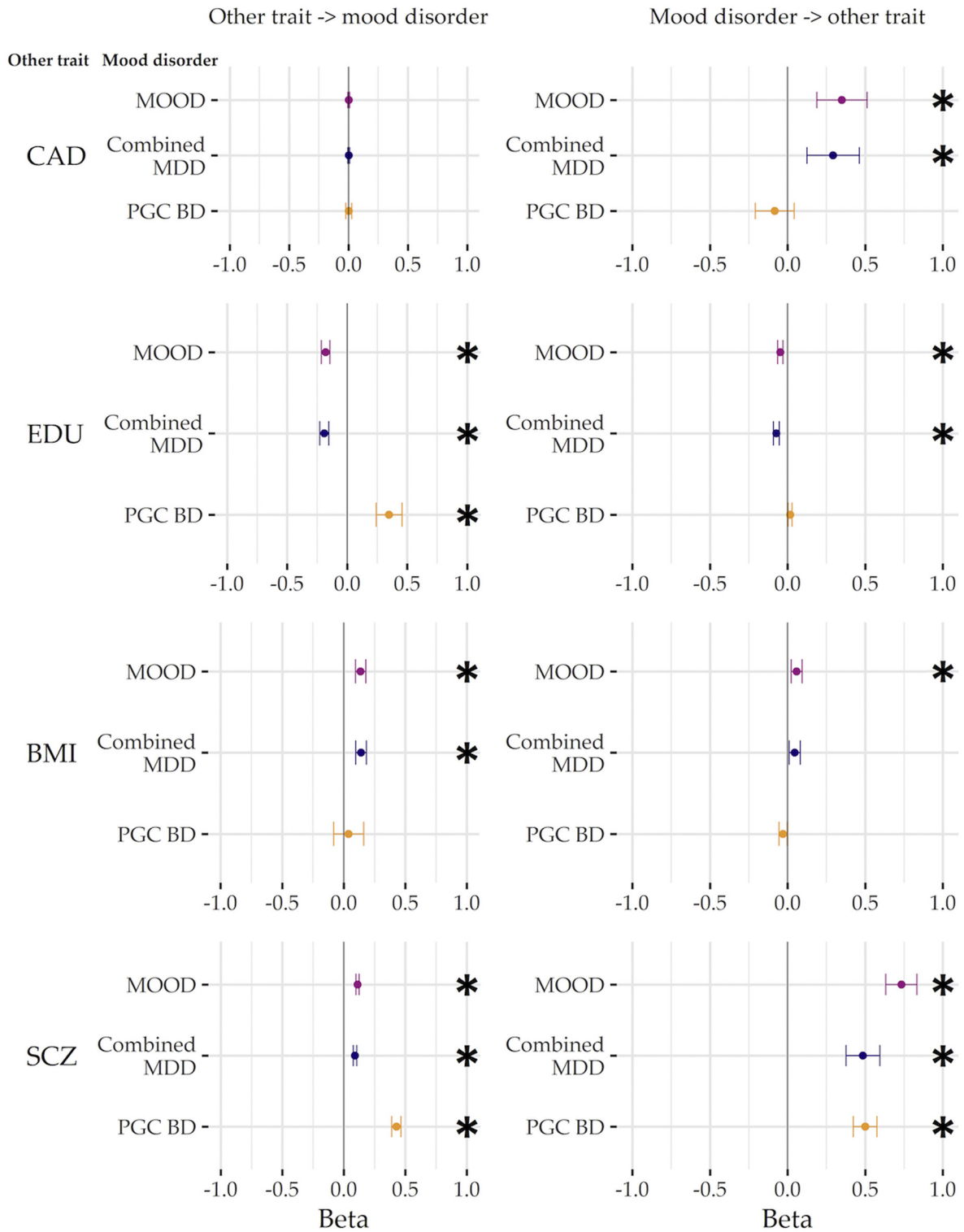


Figure 5. Generalized summary-based Mendelian randomization results from analyses with the main meta-analysis (MOOD), and the major depressive disorder and bipolar disorder analyses (combined major depressive disorder [combined MDD] cohort and Psychiatric Genomics Consortium bipolar disorder [PGC BD] cohort). External traits are coronary artery disease (CAD), educational attainment (EDU), body mass index (BMI), and schizophrenia (SCZ). β values are on the scale of the outcome genome-wide association study (logit for binary traits, phenotype scale for continuous). *$p < .004$ (Bonferroni correction for 2-way comparisons with 6 external traits). For figure data, including the number of nonpleiotropic single nucleotide polymorphisms included in each instrument, see Table S12 in Supplement 2.

potentially confounding the results of Mendelian randomization. That said, our results are consistent with a bidirectional influence of educational attainment on risk for mood disorders (and vice versa), with different directions of effect in major depressive disorder and bipolar disorder. We found no significant relationship between intelligence and either mood disorder. We also find results consistent with major depressive disorder increasing the risk for coronary artery disease in a relatively well-powered analysis. This mirrors epidemiological findings, although the mechanism remains unclear (66).

Despite the presence of depressive episodes, the mood disorders are diagnostically distinct, with differing epidemiology—for example, more women than men experience major depressive disorder, whereas diagnoses of bipolar disorder are roughly equal between the sexes (3). Differences in our genetic results between major depressive disorder and bipolar disorder may result from epidemiological heterogeneity rather than distinct biological mechanisms (67). Deeper phenotyping of GWAS datasets is ongoing, and such work will enable the effect of such confounding factors to be estimated in future studies (68).

We extend previous findings showing genetic continuity across the mood disorders (15–17,56). Combined mood disorder analyses may increase variant discovery, as well as the discovery of shared and distinct neurobiological gene sets and cell types. Our results indicate some genetic differences between major depressive disorder and bipolar disorder, including opposite bidirectional relationships of each with educational attainment, a possible influence of major depressive disorder on coronary artery disease risk, and differing mouse brain cell types implicated by the enrichment patterns of associated genes in each disorder. Finally, our data are consistent with a genetic mood disorder spectrum with separate clusters for type 1 bipolar disorder and for depressive disorders, linked by type 2 bipolar disorder, and with depression as the common symptom. The identification of specific sets of genetic variants differentially associated with depression and with mania remains an aim for future research.

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