Title: The genetics of the mood disorder spectrum: genome-wide association analyses of over 185,000 cases and 439,000 controls

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Abstract

Background

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

Methods

To clarify their shared molecular genetic basis, and to highlight disorder-specific associations, we meta-analysed data from the latest Psychiatric Genomics Consortium (PGC) 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; non-overlapping N = 609,424).

Results

Seventy-three loci reached genome-wide significance in the meta-analysis, including 15 that are novel for mood disorders. More genome-wide significant loci from the PGC analysis of major depression than 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 – positive in bipolar disorder but negative in major depressive disorder.

Conclusions

The mood disorders share several genetic associations, and can be combined effectively to increase variant discovery. However, we demonstrate several differences between these disorders. Analysing subtypes of major depressive disorder and bipolar disorder provides evidence for a genetic mood disorders spectrum.

Introduction

Mood disorders affect 10-20% of the global population across their lifetime, ranging from brief, mild episodes to severe, incapacitating conditions that markedly impact lives (1–4). Major depressive disorder and bipolar disorder are the most common forms and have been grouped together since the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (5). Although given dedicated chapters in DSM5, they remain grouped as mood disorders in the International Classification of Disorders (ICD11) (6, 7).

Depressive episodes are common to major depressive disorder and type 2 bipolar disorder, and 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 and hypomania in type 2 (7). However, these distinctions are not absolute – some individuals with major depressive disorder may later develop bipolar disorder, and some endorse (hypo)manic symptoms (8–10). Following their first depressive episode, a non-remitting individual might develop recurrent major depressive disorder or bipolar 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 35-45% of variance in risk for major depressive disorder and 65-70% of the variance in bipolar disorder risk is accounted for by additive genetic factors (13). These genetic components are partially shared, with a twin genetic correlation (r_g) of ~65%, and common variant based r_g derived from the results of genome-wide association studies (GWAS) of 30-35% (14–17). Considerable progress has been made in identifying specific genetic variants that

underlie genetic risk. Recently, the Psychiatric Genomics Consortium (PGC) published a GWAS of bipolar disorder, including over 20,000 cases, with 30 genomic loci reaching genome-wide significance (16). They also performed a GWAS of major depression, including over 135,000 individuals with major depressive disorder and other definitions of depression, with 44 loci reaching genome-wide significance (15). The PGC GWAS of major depression has since been combined with a broad depression GWAS (Supplementary Note).

GWAS have identified statistical associations with major depressive disorder and with bipolar disorder individually, but have not explored the genetic aspects of the relationship between these disorders. In addition, both major depressive disorder and bipolar disorder exhibit considerable clinical heterogeneity and can be separated into subtypes. For example, the DSM5 includes categories for bipolar disorder type 1 and type 2, and for single episode and recurrent major depressive disorder (7). We use the PGC analyses of major depression and bipolar disorder, along with analyses of formally-defined major depressive disorder from UK Biobank, to explore two aims (18, 19). Firstly, we seek to identify shared and distinct mood disorder genetics by combining studies of major depressive disorder and bipolar disorder. We then explore the genetic relationship of mood disorders to traits from the wider GWAS literature. Secondly, we assess the overall genetic similarities and differences of bipolar disorder subtypes (from the PGC) and major depressive disorder subtypes (from UK Biobank), through comparing their genetic correlations and polygenic risk scores from GWAS.

Materials and Methods

Participants

Our primary aim was to combine analyses of bipolar disorder and major depression to examine the shared and distinct genetics of these disorders. Summary statistics were derived from participants of Western European ancestries. Full descriptions of each study and their composite cohorts are provided in each paper (15, 16, 19). Brief descriptions are provided in the Supplementary Methods. Except where otherwise specified, summary statistics are available (or will be made available) at https://www.med.unc.edu/pgc/results-and-downloads.

Major depression data were drawn from the full cohort (PGC MDD: 135,458 cases, 344,901 controls) from (15). This included data from 23andMe (20), access to which requires a Data Transfer Agreement; consequently, the data analysed here differ from the summary statistics available at the link above. 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).

Secondly, 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: 3,421 cases, 22,155 controls), and for schizoaffective bipolar disorder (SAB: 977 cases, 8,690 controls), a mood disorder including psychotic symptoms. Controls are shared across these subtype analyses.

Subtype GWAS are not yet available from PGC MDD. As such, 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 DSM-5, as described in full elsewhere (18), and in Supplementary Table 1 (7). We defined three major depressive disorder subtypes for analysis. Individuals meeting criteria for major depressive disorder were classed as recurrent cases if they reported multiple depressed periods across their lifetime (rMDD, N = 17,451), and single-episode cases otherwise (sMDD, N = 12,024, Supplementary Table 1). Individuals reporting depressive symptoms, but not meeting case criteria, were excluded from the main analysis but used as a "sub-threshold depression" subtype to examine the continuity of genetic associations with major depressive disorder below clinical thresholds (subMDD, N = 21,596). All subtypes were analysed with the full set of controls. Details on the quality control and analysis of the UK Biobank phenotypes is provided in the Supplementary Methods.

Meta-analysis of GWAS data

We meta-analysed PGC MDD and UKB MDD to obtain a single major depressive disorder GWAS (combined MDD). We meta-analysed combined MDD with PGC BD, comparing mood disorder cases to controls (MOOD). Further meta-analyses were performed between PGC MDD and each bipolar disorder subtype and major depressive disorder subtype to assess the relative increase in variant discovery when adding different mood disorder definitions to PGC MDD (Supplementary Results).

Summary statistics were limited to common variants (MAF > 0.05; Supplementary Methods) either genotyped or imputed with high confidence (INFO score > 0.6) in all studies. Controls were shared between PGC MDD and PGC BD,

and (due to the inclusion of summary data in PGC MDD) 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 (Supplementary Methods). For later analyses (particularly linkage disequilibrium score regression) we used as the sample size a "non-overlapping N" estimated for each meta-analysis (Supplementary Methods). The definition, annotation and visualisation of each meta-analysis is described in the Supplementary Materials.

Sensitivity analysis using down-sampled PGC MDD

Results from MOOD showed greater similarity to PGC MDD than to PGC BD. Cross-trait meta-analyses may be biased if the power of the composite analyses differs substantially (23, 24). The mean chi-square of combined MDD [1.7] exceeded that of PGC BD [1.39], suggesting this bias may affect our results (Supplementary Table 2). We therefore repeated our analyses, meta-analysing 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 down-sampled analyses, with the exception of GSMR analyses. Full results of the down-sampled analyses are described in the Supplementary Materials.

Estimation of SNP-based heritability captured by common variants and genetic correlations with published GWAS

The SNP-based heritability captured by common variants was assessed using linkage disequilibrium score regression (LDSC) for each meta-analysed set of data

(25). SNP-based heritability estimates were transformed to the liability scale, assuming population prevalences of 15% for combined MDD, 1% for PGC BD, and 16% for MOOD, and lower and upper bounds of these prevalences for comparison (Supplementary Methods). LDSC separates genome-wide inflation into components due to polygenicity and confounding (25). Inflation not due to polygenicity was quantified as (intercept-1)/(mean observed chi-square-1) (26). Genetic correlations were calculated in LDSC between each analysis and 414 traits curated from published GWAS. Local estimates of SNP-based heritability and genetic covariance were obtained using HESS v0.5.3b (Supplementary Methods and Results) (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, SAB), and major depressive disorder subtypes (rMDD, sMDD, subMDD). Putative differences between genetic correlations were identified using a z-test ($p < 0.05$), and formally tested by applying a block-jackknife, with Bonferroni correction for significance ($p < 8.3 \times 10^{-4}$; Supplementary Methods). Differences between the genetic correlations of PGC MDD and each bipolar disorder subtype, and between PGC BD and each major depressive disorder subtype were also tested (Bonferroni correction for significance, $p < 0.0083$). Genetic correlations were hierarchically clustered using the gplots package in R v1.4.1 (29, 30). Hierarchical clustering was performed using just the subtypes, and including results from six external GWAS relevant to mood disorders (Supplementary Methods). To validate our conclusion of a genetic mood disorder spectrum, we performed principal component analysis of the genetic correlation matrix including the six external GWAS (Supplementary Methods and Results).

Association of PGC BD polygenic risk scores with major depressive disorder subtypes

Polygenic risk score analyses were performed using PRSice2 to assess whether rMDD was genetically more similar to PGC BD than were sMDD or subMDD (Supplementary Methods) (36).

Gene-wise, gene-set, and tissue and single-cell enrichment analyses

For all analyses, gene-wise p-values were calculated as the aggregate of the mean and smallest p-value of SNPs annotated to Ensembl gene locations using MAGMA v1.06 (Supplementary Methods and Results) (37). Gene set analysis was performed in MAGMA (Supplementary Methods and Results). 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 (Supplementary Methods) (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 the Supplementary Tables.

Mendelian randomisation (GSMR)

Bidirectional Mendelian randomisation 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, the relationship between the mood disorder analyses (MOOD, combined MDD, PGC BD) and schizophrenia, intelligence, educational attainment, body mass index, and coronary artery disease were explored (Supplementary Methods) (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 (Supplementary Methods) (41, 42). Analyses were performed on combined MDD conditional on PGC BD, and on PGC BD conditional on combined MDD (Supplementary Results). 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 (Supplementary Methods and Results).

Results

Evidence for confounding in meta-analyses

Meta-analysis results were assessed for genome-wide inflation of test statistics using LDSC (25). The LDSC intercept was significantly >1 in most cases (1.00-1.06), which has previously been interpreted as confounding (Supplementary Table 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%, Supplementary Table 2).

Combined MOOD meta-analysis

We meta-analysed the PGC MDD, PGC BD and the UKB MDD cohorts (MOOD, cases = 185,285, controls = 439,741, non-overlapping N = 609,424). 73 loci reached genome-wide significance, of which 55 were also seen in the meta-analysis of PGC MDD and UKB MDD (combined MDD, Supplementary Table 3, Supplementary Figures 1 and 2). Results are summarised in Table 1: 39 of the 44 PGC MDD loci reached genome-wide significance in MOOD (Supplementary Table 3, Supplementary Figures 1-8). In comparison, only four of the 19 PGC BD loci reached genome-wide significance in MOOD. MOOD loci overlapped considerably with previous studies of depression and depressive symptoms (51/73) (20, 23, 48–52), bipolar disorder (3/73) (53–56), neuroticism (32/73) (23, 57–59), and schizophrenia (15/73) (32, 60), although participants overlap between MOOD and 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 two other loci from this study did not replicate (51). Six of the 73 associations are entirely novel ($p > 5x10^{-8}$ in previous studies of all phenotypes; Table 1, Supplementary Table 4).

The down-sampled MOOD (cases = 95,481, controls = 287,932, non-overlapping N = 280,214) showed increased similarity to PGC BD compared to MOOD, but remained more similar to PGC MDD. Nineteen loci reached genome-wide significance in down-sampled MOOD, including nine (20%) from PGC MDD, compared with two (11%) reported in PGC BD (Supplementary Table 3). 17/19 loci were also observed in MOOD. Of the two loci not observed in MOOD, one passed genome-wide significance in PGC BD.

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p	Previous report
1	1	37192741	rs1002656	T	C	0.97	0.005	$2.71x10^{-11}$	DO, N
2	1	72837239	rs7531118	T	C	0.96	0.004	$1.05x10^{-16}$	D, DO, S, O
4	1	80795989	rs6667297	A	G	0.97	0.005	$5.86x10^{-11}$	D, DO
5	1	90796053	rs4261101	A	G	0.97	0.005	$1.78x10^{-8}$	D
6	1	175913828	rs10913112	T	C	0.97	0.005	$1.46x10^{-10}$	DO, O
7	1	177370033	rs16851203	T	C	0.96	0.007	$2.38x10^{-9}$	DO, S, O
9	2	22582968	rs61533748	T	C	0.97	0.004	$3.84x10^{-11}$	DO, N
10	2	57987593	rs11682175	T	C	0.97	0.004	$2.18x10^{-11}$	D, DO, BS, N, S, O
11	2	157111313	rs1226412	T	C	1.03	0.005	$1.27x10^{-8}$	D, DO, N, O
12	2	198807015	rs1518367	A	T	0.97	0.005	$1.18x10^{-8}$	BS, S, O
13	3	108148557	rs1531188	T	C	0.96	0.006	$1.61x10^{-9}$	O
14	3	158107180	rs7430565	A	G	0.97	0.004	$2.30x10^{-11}$	D, DO, N, O
16	4	42047778	rs34215985	C	G	0.97	0.006	$1.72x10^{-10}$	D, DO, N
17	5	77709430	rs4529173	T	C	0.97	0.005	$4.29x10^{-9}$	O
18	5	88002653	rs447801	T	C	1.03	0.004	$2.29x10^{-10}$	D, DO, N, O
19	5	92995013	rs71639293	A	G	1.03	0.005	$5.85x10^{-9}$	DO, N
20	5	103904226	rs12658032	A	G	1.04	0.005	$2.19x10^{-16}$	D, DO, N, O
21	5	106603482	rs55993664	A	C	0.97	0.006	$1.87x10^{-8}$	NOVEL LOCUS
22	5	124251883	rs116755193	T	C	0.97	0.005	$1.47x10^{-10}$	D, O
23	5	164523472	rs11135349	A	C	0.97	0.004	$2.96x10^{-11}$	D, DO, N
24	5	166992078	rs4869056	A	G	0.97	0.005	$5.21x10^{-9}$	D
25	6	28673998	rs145410455	A	G	0.94	0.007	$7.17x10^{-18}$	D, DO, BO, BS, DS, N, S, O
26	6	101339400	rs7771570	T	C	0.97	0.004	$9.68x10^{-10}$	DO, N, O
27	6	105365891	rs1933802	C	G	0.98	0.004	$1.05x10^{-8}$	DO, S, O
28	7	12267221	rs4721057	A	G	0.97	0.004	$7.31x10^{-11}$	D, DO, N, O
29	7	24826589	rs79879286	C	G	1.04	0.006	$1.97x10^{-11}$	B, BS, DO, S
30	7	82514089	rs34866621	T	C	1.03	0.005	$2.21x10^{-8}$	DO, O
31	7	109099919	rs58104186	A	G	1.03	0.004	$7.12x10^{-9}$	D, DO

34	9	11379630	rs10959753	T	C	0.96	0.005	$1.45x10^{-13}$	D, DO, N, O
35	9	37207269	rs4526442	T	C	0.96	0.006	$7.97x10^{-11}$	DO, O
36	9	81413414	rs11137850	A	G	1.03	0.005	$1.25x10^{-8}$	NOVEL LOCUS
38	9	119733380	rs10759881	A	C	1.03	0.005	$8.56x10^{-9}$	D, DO
40	9	122664468	rs10818400	T	G	0.98	0.004	$1.29x10^{-8}$	N
41	9	126682068	rs7029033	T	C	1.04	0.008	$2.61x10^{-8}$	D, DO, O
42	10	104684544	rs78821730	A	G	0.96	0.007	$2.95x10^{-8}$	N, BS, S, O
43	10	106563924	rs61867293	T	C	0.96	0.005	$5.64x10^{-12}$	D, DO, N, O
44	11	16293680	rs977509	T	C	0.97	0.005	$1.19x10^{-8}$	DO, N, O
45	11	31850105	rs1806153	T	G	1.03	0.005	$2.81x10^{-9}$	D, DO, N, O
46	11	32765866	rs143864773	T	C	1.04	0.008	$1.70x10^{-8}$	NOVEL LOCUS
47	11	61557803	rs102275	T	C	0.97	0.005	$5.04x10^{-11}$	B, DO, BO, O
48	11	63632673	rs10792422	T	G	0.98	0.004	$2.18x10^{-8}$	O
49	11	88743208	rs4753209	A	T	0.97	0.004	$4.15x10^{-9}$	DO, N, O
50	11	99268617	rs1504721	A	C	0.98	0.004	$2.24x10^{-8}$	O
51	11	113392994	rs2514218	T	C	0.97	0.005	$3.22x10^{-10}$	DO, BS, N, S, O
52	12	2344644	rs769087	A	G	1.03	0.005	$3.27x10^{-8}$	B, BD, BO, DS, BS, S, O
53	12	23947737	rs4074723	A	C	0.97	0.004	$3.18x10^{-9}$	D, DO, N, O
54	12	121186246	rs58235352	A	G	0.95	0.009	$1.64x10^{-10}$	DO, O
55	12	121907336	rs7962128	A	G	1.02	0.004	$3.63x10^{-8}$	NOVEL LOCUS
56	13	44327799	rs4143229	A	C	0.95	0.008	$2.73x10^{-10}$	D
57	13	53625781	rs12552	A	G	1.04	0.004	$1.25x10^{-23}$	D, DO, O
58	14	42074726	rs61990288	A	G	0.97	0.004	$2.29x10^{-10}$	D, DO, O
60	14	64686207	rs915057	A	G	0.98	0.004	$1.92x10^{-8}$	D, DO, O
61	14	75130235	rs1045430	T	G	0.97	0.004	$9.83x10^{-11}$	D, DO, N, O
62	14	104017953	rs10149470	A	G	0.97	0.004	$1.15x10^{-10}$	D, DS, DO, BS, S, O
63	15	36355868	rs1828385	A	C	0.97	0.004	$1.15x10^{-8}$	NOVEL LOCUS
64	15	37643831	rs8037355	T	C	0.97	0.004	$4.09x10^{-15}$	D, DO, O
65	16	6310645	rs8063603	A	G	0.97	0.005	$5.36x10^{-11}$	D, DO

66	16	7667332	rs11077206	C	G	1.03	0.004	$5.49x10^{-10}$	D, DO, N, O
67	16	13038723	rs12935276	T	G	0.97	0.005	$4.75x10^{-10}$	D, DO, N, O
68	16	13750257	rs7403810	T	G	1.03	0.005	$7.52x10^{-11}$	DO, BS, S, O
69	16	72214276	rs11643192	A	C	1.03	0.004	$1.46x10^{-11}$	D, O
70	17	27363750	rs75581564	A	G	1.04	0.006	$2.47x10^{-10}$	D, DO, O
71	18	31349072	rs4534926	C	G	1.03	0.004	$9.14x10^{-9}$	DO, N
72	18	36883737	rs62099069	A	T	0.97	0.004	$9.52x10^{-10}$	D, O
73	18	42260348	rs117763335	T	C	0.97	0.005	$1.33x10^{-8}$	O
74	18	50614732	rs11663393	A	G	1.03	0.004	$1.56x10^{-10}$	D, DO, N, O
75	18	52517906	rs1833288	A	G	1.03	0.005	$4.54x10^{-8}$	D, DS, DO, N, S, O
76	18	53101598	rs12958048	A	G	1.04	0.005	$4.86x10^{-14}$	D, DO, BS, N, S, O
77	19	30939989	rs33431	T	C	1.02	0.004	$4.04x10^{-8}$	DO, O
78	20	45841052	rs910187	A	G	0.97	0.005	$3.09x10^{-9}$	DO, O
79	22	41621714	rs2179744	A	G	1.03	0.005	$3.83x10^{-12}$	D, B, DO, BS, N, S, O
80	22	42815358	rs7288411	A	G	1.03	0.005	$3.86x10^{-8}$	NOVEL LOCUS
81	22	50679436	rs113872034	A	G	0.96	0.006	$1.10x10^{-9}$	O

Table 1: Loci genome-wide significant ($p < 5x10^{-8}$) in the MOOD meta-analysis.

Locus – shared locus number for annotation (Supplementary Table 3), Chr – chromosome, BP – base position, A1 – effect allele, A2 – non-effect allele, Previous report – locus previously implicated in PGC MDD (D), PGC BD (B), previous combined studies of bipolar disorder and major depressive disorder (BD), other studies of major depressive disorder or depressive symptoms (DO), other studies of bipolar disorder (BO), previous combined studies of bipolar disorder and schizophrenia (BS), previous combined studies of major depressive disorder and schizophrenia (DS), neuroticism (N), schizophrenia (S), or other studies (O – see Supplementary Table 4).

SNP-based heritability and genetic correlations

The estimate of SNP-based heritability for MOOD (8.8%) was closer to PGC MDD (9%) than to PGC BD (17-23%) (15, 16). Significant genetic correlations between MOOD and other traits included psychiatric and behavioural, reproductive, cardiometabolic, and sociodemographic traits (Figure 1, Supplementary Table 5). Genetic correlations with psychiatric and behavioural traits are consistently observed across psychiatric traits (17, 61). The genetic correlation with educational attainment differs, being negative in combined MDD, but positive in PGC BD (Supplementary Table 6). The genetic correlation (r_g) between MOOD and educational attainment was -0.058 (p=0.004), intermediate between the results of combined MDD and of PGC BD. Notably, the genetic correlation with intelligence (IQ) was not significant in combined MDD, PGC BD, nor MOOD ($p>1.27x10^{-4}$). However, sensitivity analyses (see below), indicated that including 23andMe in the PGC MDD sample obscured a negative genetic correlation of MDD with IQ.

The SNP-based heritability of down-sampled MOOD from LDSC was 11%, closer to PGC MDD than to PGC BD (Supplementary Table 2). Genetic correlations varied (Supplementary Tables 5 and 7) with some more similar to PGC BD (schizophrenia: down-sampled rg = 0.61, combined MDD rg = 0.35, PGC BD rg = 0.7), and others more similar to combined MDD (ADHD: down-sampled rg = 0.48, combined MDD rg = 0.45, PGC BD rg = 0.14). The genetic correlation with IQ was significant (rg = -0.13, $p = 5x10^{-7}$), because the excluded 23andMe depression cohort has a positive genetic correlation with IQ (rg = 0.06, p = 0.01). The greater genetic correlation of MOOD with combined MDD (0.98) compared to PGC BD (0.55) persisted when comparing down-sampled MOOD to combined MDD (0.85) and PGC BD (0.75; Supplementary Table 6).

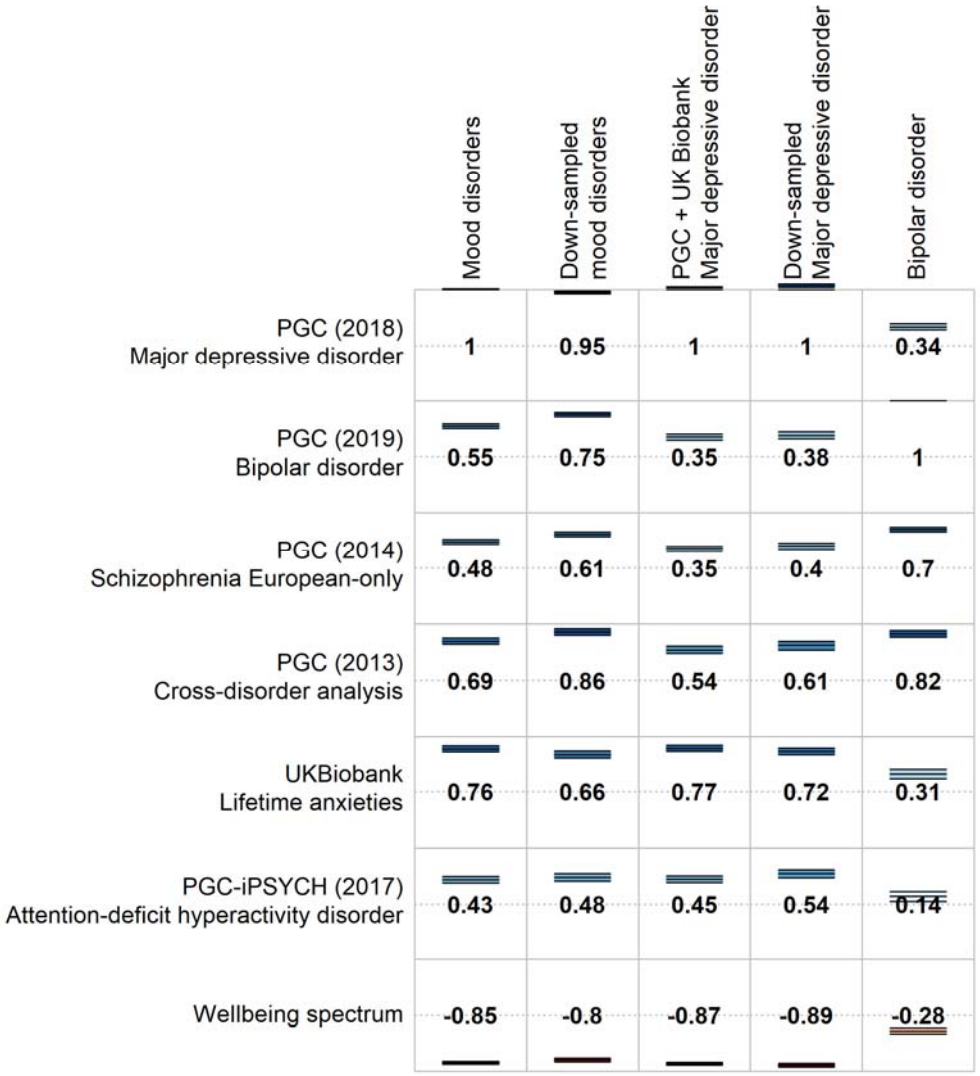

Figure 1a: Selected genetic correlations of psychiatric traits with the main meta-analysis (MOOD), the separate mood disorder analyses (combined MDD and PGC BD), and the down-sampled analyses (down-sampled MOOD, down-sampled MDD). Full genetic correlation results are provided in Supplementary Table 5.

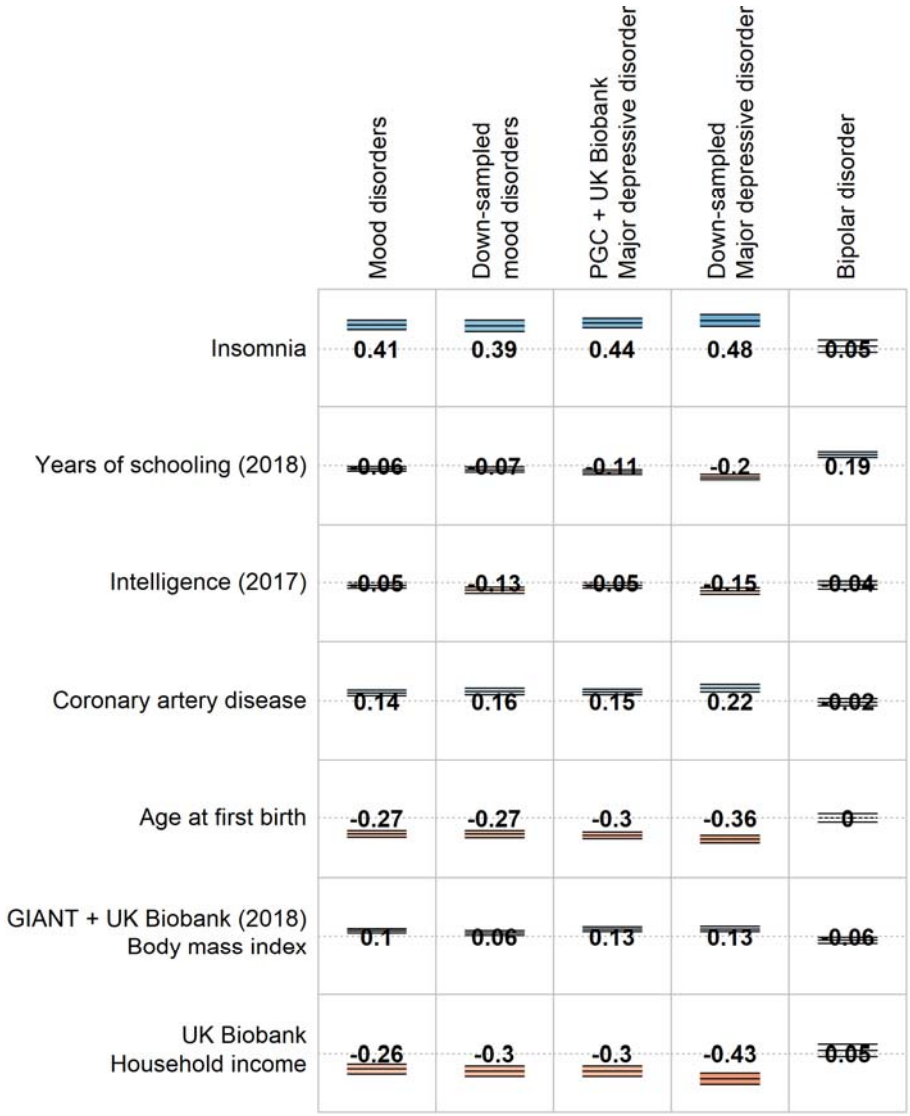

Figure 1b: Selected genetic correlations of other traits with the main meta-analysis (MOOD), the separate mood disorder analyses (combined MDD and PGC BD), and the down-sampled analyses (down-sampled MOOD, down-sampled MDD). Full genetic correlation results are provided in Supplementary Table 5.

Relationship between mood disorder subtypes

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

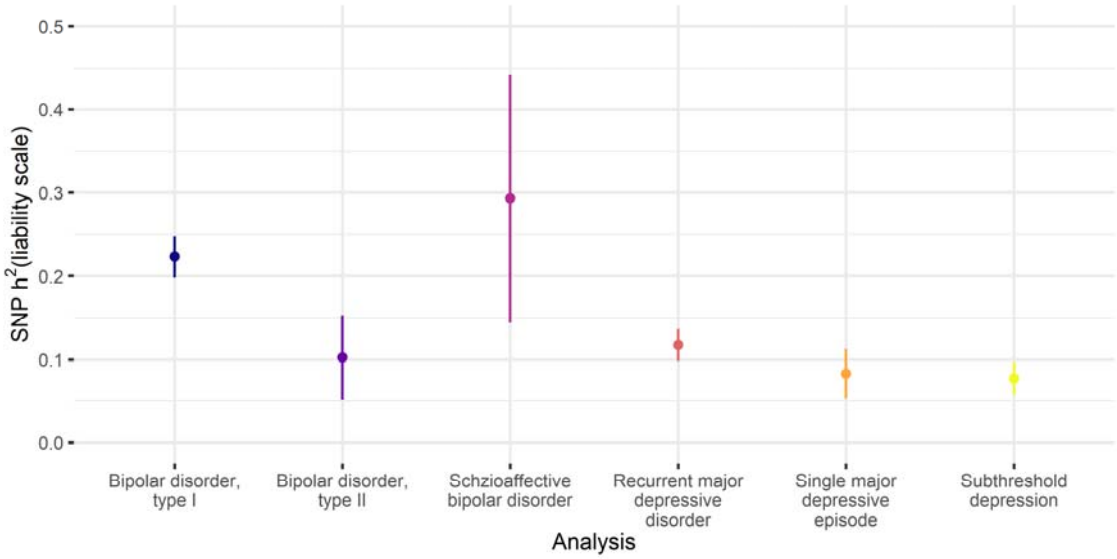

Figure 2: SNP-based heritability estimates for the subtypes of bipolar disorder and subtypes of major depressive disorder. Points = SNP-based heritability estimates. Lines = 95% confidence intervals. Full SNP-based heritability results are provided in Supplementary Table 2.

The major depressive disorder subtypes were strongly and significantly genetically correlated (r_g = 0.9-0.94, $p_{rg = 0} < 8.3x10^{-4}$). These correlations did not differ significantly from 1 (all $p_{rg = 1} > 0.3$), nor from each other (all $p_{\Delta rg = 0} > 0.5$, Figure 2, Supplementary Table 8). BD1 and SAB were strongly correlated (r_g = 0.77, $p_{rg = 0}$ =

$6x10^{-13}$, $p_{rg = 1} = 0.03$), as were BD1 and BD2 ($r_g = 0.86$, $p_{rg = 0} = 3x10^{-16}$, $p_{rg = 1} = 0.2$). However, BD2 was not significantly correlated with SAB ($r_g = 0.22$, $p_{rg = 0} = 0.02$).

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 ($r_g = 0.68$, $p_{rg = 0} = 3x10^{-8}$, $p_{rg = 1} = 0.01$), following multiple testing correction ($\Delta r_g = 0.18$, $p = 0.02$). Overall, these results suggest a spectrum of genetic relationships between major depressive disorder and bipolar disorder, with BD2 bridging the two disorders (Figure 3; Supplementary Figure 9). This spectrum remained when six external phenotypes were added, and was supported by results from principal component analysis (Supplementary Results, Supplementary Figure 10).

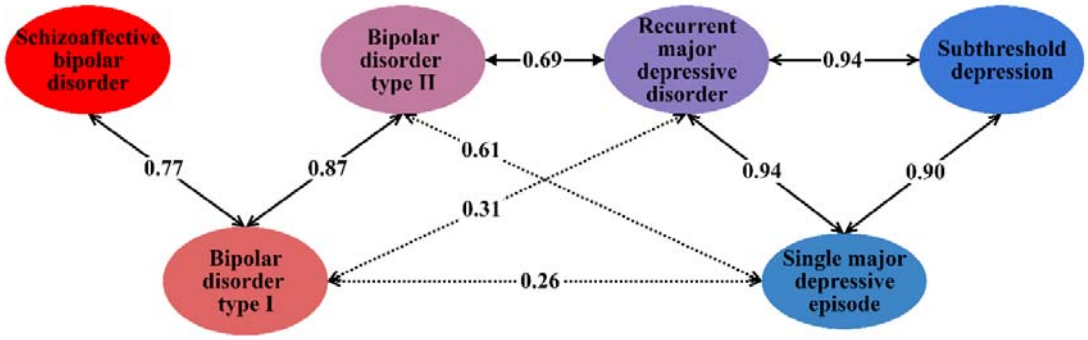

Figure 3: Genetic correlations across the mood disorder spectrum. Labelled arrows show genetic correlations significantly different from 0. Solid arrows represent genetic correlations not significantly different from 1 ($p < 0.00333$, Bonferroni correction for 15 tests). Full results are provided in Supplementary Table 8.

Polygenic risk score analyses showed that individuals with high polygenic risk scores for PGC BD were more likely to report rMDD than sMDD, and more likely to report sMDD than subMDD (Supplementary Results).

Tissue and cell-type specificity analyses

The results of gene-wise and gene set analyses are described in the Supplementary Results. The tissue-specificity of associated genes differed minimally between the analyses (Supplementary Table 9). All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in combined MDD and PGC BD ($p < 9.43 \times 10^{-4}$, Bonferroni correction for 53 regions, Supplementary Table 9). Results from down-sampled MOOD and down-sampled MDD were generally consistent with the main analyses, except spinal cord was not enriched in either, nor was the cordate in the down-sampled MDD analysis.

In contrast, cell-type enrichments differed between combined MDD and PGC BD (Figure 4, Supplementary Tables 10 and 11). Genes associated with PGC BD 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 were significant in combined MDD. Genes only associated with combined MDD were significantly enriched for expression in neuroblasts and dopaminergic neurons from adult mice. Further cell-types (dopaminergic neuroblasts; dopaminergic, GABAergic and midbrain nucleus neurons from embryonic mice; interneurons; and medium spiny neurons) were enriched for both combined MDD and PGC BD, but the rank and strength of enrichment differed, most notably for medium spiny neurons. The general pattern of differences persisted when comparing PGC BD with down-sampled MDD, although genes associated with

down-sampled MDD were not enriched for expression in adult dopaminergic neurons, embryonic midbrain nucleus neurons, interneurons, nor medium spiny neurons (Supplementary Figure 11).

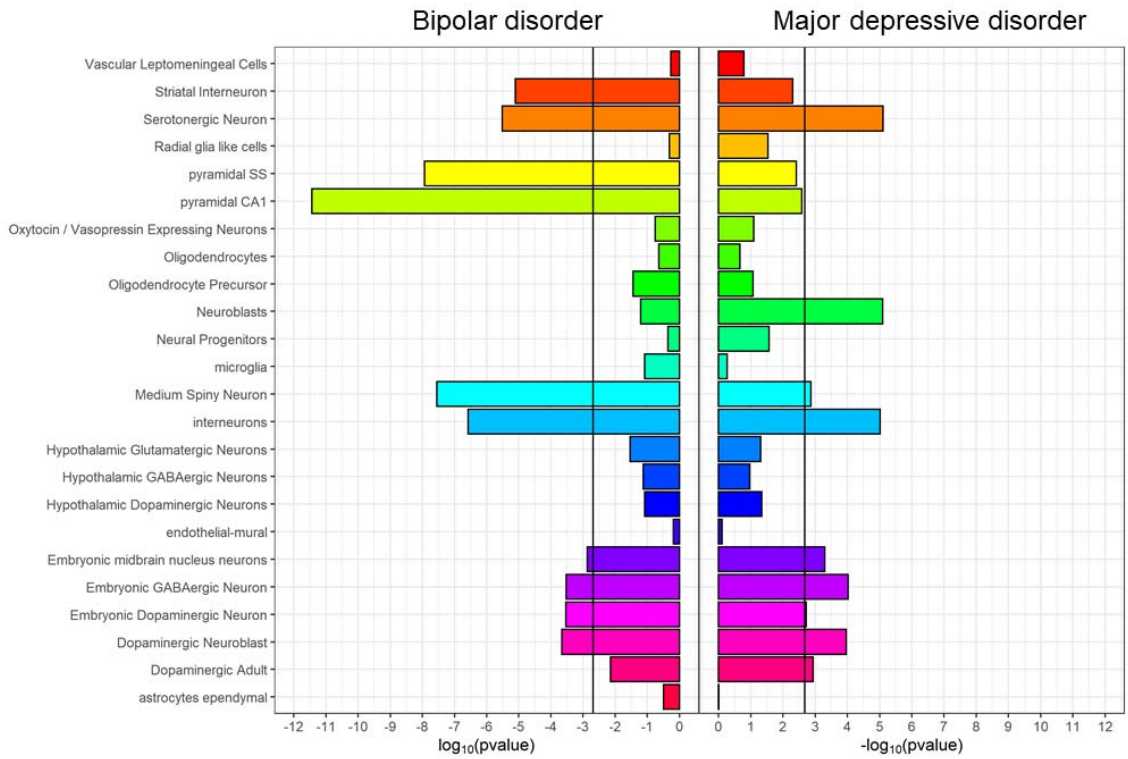

Figure 4: Cell-type expression specificity of genes associated with bipolar disorder (PGC BIP, left) and major depressive disorder (combined MDD, right). Black vertical lines = significant enrichment ($p < 2x10^{-3}$, Bonferroni correction for 24 cell types). See Supplementary Table 10 for full results.

Shared and distinct relationships with mood disorders and inferred causality

Bidirectional Mendelian randomisation was used to investigate previously-described relationships between mood disorder phenotypes (combined MDD, PGC BD) and external traits: schizophrenia, educational attainment, IQ, body mass index (BMI) and coronary artery disease (CAD; Figure 5, Supplementary Table 12). Associations with PGC BD should be interpreted cautiously, as only 19 loci reached

genome-wide significance, several of which were removed as potentially pleiotropic in the analyses below.

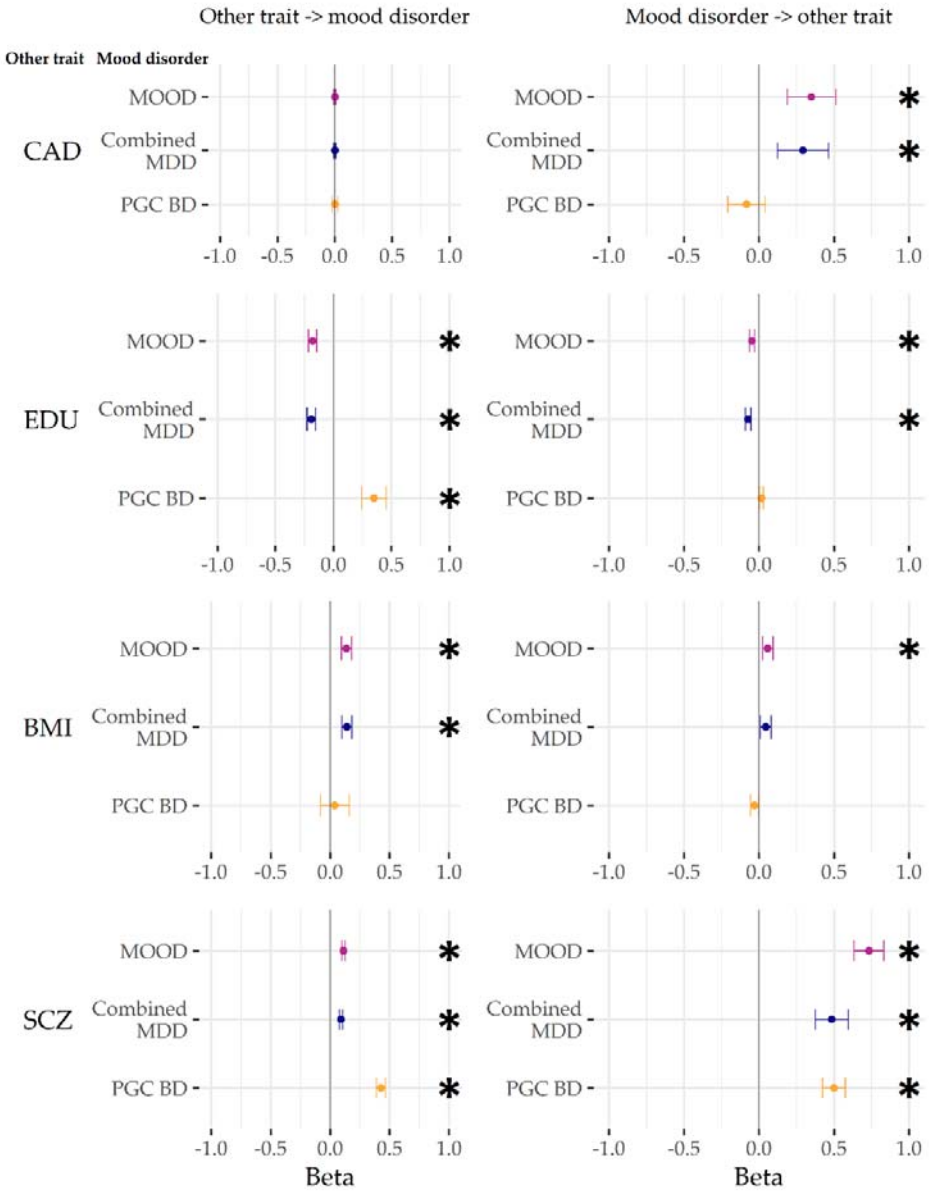

Figure 5: GSMR results from analyses with the main meta-analysis (MOOD), and the major depression and bipolar disorder analyses (combined MDD, PGC BD). External traits are coronary artery disease (CAD), educational attainment (EDU), body mass index (BMI), and schizophrenia (SCZ). Betas are on the scale of the outcome GWAS (logit for binary traits, phenotype scale for continuous). * $p < 0.004$ (Bonferroni correction for two-way comparisons with six external traits). For figure data, including the number of non-pleiotropic SNPs included in each instrument, see Supplementary Table 12.

A positive bidirectional relationship was observed between combined MDD and PGC BD, and between schizophrenia and both combined MDD and PGC BD. This is consistent with psychiatric disorders acting as causal risk factors for the development of further psychiatric disorders, or being correlated with other causal risk factors, including (but not limited to) the observed shared genetic basis.

The relationship with educational years differed between the mood disorders – there was a negative bidirectional relationship between educational years and 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 IQ. This is consistent with differing causal roles of education (or correlates of education) on the mood disorders, with a weaker reciprocal effect of the mood disorders altering the length of education.

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

Discussion

We identified 73 genetic loci by meta-analysing cohorts of major depression and bipolar disorder, including 15 loci novel to mood disorders. Our overall mood disorders meta-analysis results (MOOD) have more in common with our major depressive disorder analysis (combined MDD) than our bipolar disorder analysis (PGC BD). Partly, this results from the greater power of the major depressive disorder analysis compared to the bipolar disorder analysis. Nevertheless, genetic

associations from our sensitivity analysis with equivalently powered cohorts (using down-sampled MDD in place of combined MDD) still showed a greater overall similarity to those from major depressive disorder rather than bipolar disorder.

This 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 (or psychosis) may have higher effect sizes, detectable at current bipolar disorder GWAS sample sizes, and may not be strongly associated with major depressive disorder. This could contribute to the observed higher heritability of bipolar disorder compared to major depressive disorder, and agrees with reports that most of the genetic variance for mania is not shared with depression (13, 14). In this case, meta-analysis of bipolar disorder and major depressive disorder cohorts would support variants associated more with depression, but not those associated more 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 assessed genetic correlations between mood disorder subtypes. We observed high, consistent correlations between major depressive disorder subtypes, including sub-threshold depression. Bipolar disorder type 2 showed greater genetic similarity to major depressive disorder compared to type 1. In this, we build on similar findings from polygenic risk scores analyses (16, 56). Individuals with high polygenic risk scores for PGC BD were more likely to report recurrent than single-episode major depressive disorder. However, the genetic correlation of PGC BD with recurrent major depressive disorder was not significantly greater than that with single-episode major depressive disorder. This might reflect the difference in power between these methods. We also examined the genetic correlations between mood

disorder subtypes in the context of relevant external traits (Supplementary Results). Our subtype analyses support a genetic mood spectrum consisting of the schizophrenia-like bipolar disorder type 1 and schizoaffective disorder at one pole, and the depressive disorders at the other, with bipolar disorder type 2 occupying an intermediate position.

Conditional and reversed-effect analyses (Supplementary Results) suggest that few of the loci we identified are disorder-specific. However, our results highlight some differences between the genetics of the mood disorders. The expression specificity of associated genes in mouse brain cell types differed between bipolar disorder and major depressive disorder analyses. 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 GABAergic neurons) had weaker enrichments in schizophrenia, but were enriched in analyses of neuroticism (57). The higher rank of the enrichment of serotonergic neurons with major depressive disorder compared to bipolar disorder is striking given the use of drugs targeting the serotonergic system in the treatment of depression (63). Nevertheless, cell-type enrichment analyses are still novel, and require cautious interpretation, especially given the use of non-human reference data (38, 64).

We explored potential causal relationships between the mood disorders and other traits using Mendelian randomisation. The interpretation of these analyses is challenging, especially for complex traits, when the ascertainment of cases varies, and when there are relatively few (< 20) variants used as instruments (for example, in the PGC BD and down-sampled analyses presented) (41, 67, 68). Major depressive disorder and bipolar disorder demonstrate considerable heterogeneity

(as our subtype analyses show for bipolar disorder types 1 and 2), potentially confounding the results of Mendelian randomisation. That said, our analyses are consistent with a bidirectional influence of educational attainment on risk for mood disorders (and vice versa), with different directions of effect in the two mood disorders. We found no significant relationship between IQ 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 (69).

Despite the presence of depressive episodes, the mood disorders are diagnostically distinct. This is reflected in their differing epidemiology – for example, more women than men suffer from 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 (70). Deeper phenotyping of GWAS datasets is ongoing, and will enable the effect of confounding factors such as sex to be estimated in future studies (71).

We extend previous findings showing genetic continuity across the mood disorders (15–17, 56). Combined analyses of major depressive disorder and bipolar disorder may increase variant discovery, as well as the discovery of shared and distinct neurobiological gene sets and cell types. Our results also indicate some genetic differences between major depressive disorder and bipolar disorder, including opposite bidirectional relationships of each mood disorder 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

the existence of a genetic mood disorder spectrum with separate clusters for bipolar disorder type 1 and depressive disorders, linked by bipolar disorder type 2, and with depression as the common symptom. The mood disorders have a partially genetic aetiology that is partly shared. 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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Data availability

GWAS results from analyses including 23andMe are restricted by a data transfer agreement with 23andMe. For these analyses, LD-independent sets of 10,000 SNPs will be made available via the Psychiatric Genetics Consortium (https://www.med.unc.edu/pgc/results-and-downloads). Summary statistics not including 23andMe will be made available via the Psychiatric Genetics Consortium (https://www.med.unc.edu/pgc/results-and-downloads).