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Abstract

Mood disorders affect 10-20% of the population, ranging from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Multiple approaches have shown considerable sharing of genetic risk factors between unipolar and bipolar mood disorders. We use data from the largest genome-wide association studies of major depression (MD) and bipolar disorder (BD) to investigate the molecular basis of the shared genetic liability to mood disorders. We meta-analysed the Psychiatric Genomics Consortium (PGC) MD and BD cohorts, and an additional MD cohort from UK Biobank (185,285 cases, 439,741 controls, non-overlapping N = 609,424). 73 loci reached genome-wide significance in the meta-analysis, with additional loci significant in subtype and depression-only analyses. More genome-wide significant loci from PGC MD (39/44, 89% of the PGC MD loci) than PGC BD (4/19, 21%) reached genome-wide significance in the meta-analysis. Genetic correlations calculated between MD and BD subtypes revealed that type II BD correlates strongly with MD. Integrating the results with systems biology information, we implicate pathways and neuronal subtypes which highlight similarities but also potential differences between MD and BD. Our results reflected MD more than BD, perhaps due to the larger sample size for MD, but also perhaps because depression is their predominant common feature. Overall, these results provide evidence for a genetic mood disorders spectrum.

Introduction

Mood disorders affect 10-20% of the global population across their lifetime and have been posited to form part of a broader spectrum of affective pathology[1–4]. They range from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Type I and type II bipolar disorder are distinguished from major depressive disorder by the presence of mania in type I and hypomania in type II[5]. However, episodes of depressive symptoms, characterised as "sad, empty, or hopeless mood", are characteristic of major depressive disorder and type II bipolar disorder, and are usually present in type I bipolar disorder[5]. The distinction between the mood disorders is not absolute, as some individuals initially diagnosed with major depressive disorder later develop bipolar disorder, and a substantial fraction of major depressive disorder cases endorse manic or hypomanic symptoms[6–8].

The mood disorders demonstrate considerable sharing of genetic risk factors, suggesting a partially common aetiopathology[9]. 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[10]. These genetic components are shared, with a twin genetic correlation (r_g) of ~= 65%, and smaller estimates (30-35%) derived from comparing the results of genome-wide association studies (GWAS) [9,11–13]. Considerable progress has been made in identifying specific genetic variants that underlie genetic risk - most recently, we published GWAS of bipolar disorder, including over 20,000 cases with 30 genomic loci reaching genome-wide significance[12], and major depression, including over 135,000 cases with 44 loci reaching genome-wide significance[11].

Here, we make use of these analyses in conjunction with analyses of major depression from UK Biobank to explore three aims[14,15]. Firstly, we meta-analyse the results of the major depression and bipolar disorder studies to identify regions of shared mood disorder genetics and explore the genetic relationship of mood disorders to published traits from the wider GWAS literature. Secondly, we compare the genetic correlations from GWAS of bipolar disorder subtypes (from the PGC) and major depression subtypes (from UK Biobank) and assess the separation of these mood disorder subtypes. Finally, we condition the meta-analysed major depression cohorts on the bipolar disorder GWAS (and vice versa) to examine how such conditioning affects genomic systems biology analyses of the results and the genetic correlations of each disorder with other traits.

Materials and Methods

Participants

Summary statistics were obtained from the most recent PGC GWAS of each disorder, involving participants of Western European ancestry. Major depression data was drawn from the full cohort (PGC MD: 135,458 cases, 344,901 controls) from Wray et al. (2018). This cohort included data from 23andMe[16], access to which is restricted by a Data Transfer Agreement - as such, it differs from the publicly-available summary statistics (available at https://www.med.unc.edu/pgc/results-and-downloads). Within this paper, PGC MD is referred to as a major depression cohort. Many individuals in the cohort met criteria for major depressive disorder through clinical ascertainment. However, others self-reported their diagnosis, and so may not have met criteria in a clinical setting - as such, it may be more appropriate to

consider these individuals as having major depression, rather than major depressive disorder.

Full access is available at the link above to GWAS summary statistics for bipolar disorder (PGC BD: 20,352 cases, 31,358 controls[12]). These summary statistics are drawn from the discovery analysis previously reported, and do not include replication results[12]. Summary statistics are also available for subset analyses examining type I bipolar disorder (BD1: 14,879 cases, 30,992 controls), type II bipolar disorder (BD2: 3,421 cases, 22,155 controls), and schizoaffective bipolar disorder (SAB: 977 cases, 8,690 controls). Full descriptions of each study and their composite cohorts are provided in each paper. Brief descriptions are provided in the Supplementary Materials.

An additional MD cohort was derived from the online mental health questionnaire in the UK Biobank (UKB MD; Resource 22 on http://biobank.ctsu.ox.ac.uk[14]). The definition of MD is described in full elsewhere, and in Supplementary Table 1[15]. In total, 29,475 cases and 63,482 controls were available for analysis (all Western European ancestry). Subsets of UKB MD were used for subtype analyses. Individuals meeting criteria for MD were classed as recurrent cases if they reported multiple depressed periods across their lifetime (rMD, N = 17,451), and single-episode cases otherwise (sMD, N = 12,024; Supplementary Table 1). A further set of individuals reported some depressive symptoms but did not meet case criteria (and so are excluded from UKB MD) and were classed as "sub-threshold" (subMD, N = 21,596). All subsets 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 Materials.

Meta-analysis

Meta-analysis was performed between PGC MD, UKB MD and PGC BD (hereafter referred to as MD-UKB-BD). Only variants present in all three studies were included in the results of the meta-analysis. Summary statistics were limited to common variants (MAF > 0.05) that were either genotyped or imputed with high confidence (INFO score > 0.6). A higher MAF threshold was chosen as previous analyses of the BD2 subset suggested the inclusion of lower MAF variants may bias heritability estimates[12].

Controls were known to be shared between the PGC MD and PGC BD analyses, and (due to the inclusion of summary data in PGC MD) the full extent of this overlap was unknown. All 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[17,18]. As later analyses (particularly LD score regression) use the total number of subjects in the analysis for calculations, a "non-overlapping N" was estimated for each meta-analysis (Supplementary Materials). Further meta-analyses were performed between PGC MD and UKB MD (MD-UKB), and between PGC MD and each PGC BD subtype and UKB MD subtype. The results and discussion of the subset meta-analyses are included in the Supplementary Materials.

Definition of GWAS loci

GWAS results were clumped using PLINK1.9[19], assigning nominally-significant ($p < 10^{-4}$) variants to a clump if they were in linkage disequilibrium ($r^2 > 0.1$ in unrelated non-Finnish European participants from 1000 Genomes project) with a

variant with a lower p-value lying within 3Mb. Loci were declared genome-wide significant if a variant in the locus reached the conventional threshold for genome-wide significance ($p = 5 \times 10^{-8}$). Results were visualised using FUMA, including mapping the loci to potentially affected genes through expression quantitative trait loci (eQTLs) and chromatin contact sites in brain tissues or neural progenitor cells[20].

All genomic loci reaching genome-wide significance in at least one analysis were combined for annotation. Where loci from different GWAS overlapped, they were combined into a single locus ranging from the minimum base position from any of the constituent loci to the maximum. Annotation was performed using RegionAnnotator version 1.63 (https://github.com/ivankosmos/RegionAnnotator), which includes data from: the NHGRI-EBI GWAS Catalog; OMIM; GENCODE genes; genes previously implicated in autism and in intellectual disability; copy-number variants previously implicated in psychiatric disorders; and mouse knockout phenotypes. Results from the GWAS Catalog module of RegionAnnotator were filtered to include only variants reaching genome-wide significance. Where multiple variants from a previous GWAS of a specific phenotype were listed as significant, only the variant with the lowest p-value is reported.

The relationship between the loci identified in the meta-analyses (MD-UKB-BD, MD-UKB) and the constituent analyses (PGC MD, UKB MD, PGC BD) was assessed using a hierarchically-clustered heatmap, with the 2014 PGC schizophrenia analysis (SCZ) included for comparison[21]. For this comparison, an index SNP was selected for each locus (the variant with the lowest p-value that was common to all four analyses) to obtain the direction of effect in each analysis. Index SNP p-values were converted to $-\log_{10}$(p-value) - if the $OR_{index} < 1$ in a given analysis, the $\log_{10}$(p-value) was used in place of the $-\log_{10}$(p-value). A hierarchically-

clustered heatmap was then generated using the default options of the heatmap.2 function of the gplots package in R v1.4.1 (complete clustering on the Euclidean distance between vectors) with clustering performed separately for rows and for columns[22,23].

Conditional analyses

Additional analyses were performed to understand which genomic loci are shared or distinct between the disorders, using mtCOJO, an extension of the GSMR method implemented in GCTA[24,25]. mtCOJO adjusts the results of a GWAS, conditioning on the effects of a set of significantly associated, independent variants from a second set of summary statistics (a putative instrumental variable). The resulting estimated effect size is robust to confounding caused by genetic or environmental effects shared between the studies analysed, assuming these are uncorrelated with the instrumental variable[24,26].

Analyses were performed on MD-UKB conditional on PGC BD (MD-UKBcBD), and on PGC BD conditional on MD-UKB (BDcMD-UKB). Variant selection for conditioning was performed with the default settings in mtCOJO, clumping using the UK Biobank dataset, and selecting at least 10 variants with $p<5x10^{-8}$, which were not in linkage disequilibrium ($r^2 < 0.05$) with a variant with a lower p-value, and which did not show evidence of pleiotropy (passed the HEIDI-outlier analysis, threshold 0.01[24]). Results were clumped in PLINK using the procedure described above for the meta-analyses.

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

The SNP-heritability captured by common variants was assessed using LD Score regression[27]. Estimates were made for each meta-analysed set of data, and SNP-heritability estimates transformed to the liability scale assuming that the combined population prevalence is the sum of the prevalence of the constituent disorders. Estimates were made assuming a population prevalence of 15% for PGC MD, 1% for PGC BD and 16% for MD-UKB-BD. Further estimates were made for the lower bounds of prevalence (MD-UKB-BD: 10.5%, assuming lower bound for PGC MD of 10%, and for PGC BD of 0.5%) and upper bounds of prevalence (MD-UKB-BD: 22%, assuming upper bound for PGC MD of 20%, and for PGC BD of 2%) for comparison.

Genetic correlations between the meta-analysis and 393 traits curated from published GWAS were calculated in LD Score. A conservative Bonferroni correction was used to determine significance ($p < 1.27 \times 10^{-4}$, approximate correction for 393 tests). Genetic correlations were compared between MD-UKB and MD-UKBcBD, and between PGC BD and BDcMD-UKB, first using a z-test to identify putative differences ($p < 0.05$), and then formally testing by applying a block-jackknife (Supplementary Methods), with a Bonferroni correction applied for these formal tests[27–29].

Genetic correlations between subset analyses

SNP heritabilities and genetic correlations were calculated in LD Score between the PGC BD subsets (BD1, BD2, SAB), and the UKB MD subsets (rMD, sMD, subMD) to assess the structure of genetic correlations across the mood

disorder spectrum. The resulting genetic correlations were then hierarchically clustered (as described above) using the gplots package in R v1.4.1[22,23].

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

For all analyses, assessed variants were annotated to Ensembl gene locations using MAGMA v1.06 (using the build 37 reference supplied on the MAGMA website[30]). SNPs were assigned to genes if they lay between 35kb upstream and 10kb downstream of the gene location[31]. Gene-wise p-values were calculated as the aggregate of the mean and smallest p-value across all SNPs annotated to the gene. MAGMA accounts for possible confounders such as gene size, gene density, linkage disequilibrium and minor allele count. The threshold for genome-wide significance was defined at $p < 2.6 \times 10^{-6}$ (Bonferroni correction for the 19,041 genes tested). Genes passing genome-wide significance were defined as coming from the same locus if they lay within 100kb of each other, or if they overlapped a locus from the single variant analysis.

Gene set analysis was performed for all analyses. A gene set matrix **P** was generated with elements $P_{g,p} = 1$ if gene g was in set p and $P_{g,p} = 0$ otherwise. Association between gene set membership and gene-wise z-scores was computed using MAGMA. 13,567 gene sets were drawn from OpenTargets (downloaded January 2017[32]), GO ontologies, canonical gene sets drawn from MSigSB v5.2 C2 and C5 datasets[33], and biological gene sets related to psychiatric disorders found in various scientific publications (links in Supplementary Materials). There is considerable overlap of genes between gene sets (within and between sources). Gene sets that overlapped entirely were treated as a single gene set in analyses. The effective number of gene sets tested was defined as the number of principal

components accounting for 99.5% of explained variance in the gene set similarity matrix, obtained by computing the Tanimoto similarity between gene sets. This results in a Bonferroni-corrected threshold of $p = 5.34 \times 10^{-6}$ for 9,361 effectively independent tests for each matrix.

Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (version 7 data from the Genotype-Tissue Expression project) and broadly-defined ("level 1") and narrowly-defined ("level 2") cell-types (Karolinska Institutet mouse brain single-cell RNA sequencing superset[34,35]). Analyses were performed in MAGMA following previously described methods with minor modifications[35]. Briefly, for the single cell data set [35], gene expression for each cell type was scaled to 10,000 unique molecular identifiers prior to computing specificity scores. Specificity scores are defined as the proportion of the total expression of a specific gene found in a given cell type. For the GTEx dataset, transcripts per million (TPM) were transformed to $\log_2(\text{TPM} + 1)$ prior to computing specificity scores. For each tissue or cell-type, the specificity scores were then rank-transformed to a standard normal distribution using the *rntranform* function from the GenABEL R package[36]. The standard normalised specificity scores were then regressed on gene-wise association from the meta-analysis, defined as the mean p-value across all SNPs assigned to the gene. Multiple-testing correction was applied using Bonferroni-correction within each analysis.

Mendelian randomisation (GSMR)

Bidirectional Mendelian randomisation analyses were performed using the GSMR option in GCTA to test the causal direction of known relationships between mood disorder traits and other traits[24,25]. Specifically the relationship between the

mood disorder analyses (MD-UKB, PGC BD, MD-UKB-BD, MD-UKBcBD and BDcMD-UKB) and PGC MD, PGC BD, schizophrenia[21], intelligence[37], educational attainment[38], body mass index[39], and coronary artery disease[40] were explored. GSMR uses a putative instrumental variable derived from the summary statistics of the trait of interest to act as a proxy for that trait in regression analyses (as described above for mtCOJO analyses). GSMR uses the HEIDI test to remove pleiotropic variants from the instrument variable set, addressing one limitation of Mendelian randomisation more broadly. All analyses were run using the default settings in GSMR, assuming at least ten linkage-independent ($r^2 < 0.05$) significant ($p<5x10^{-8}$) variants pass the HEIDI test (threshold 0.01).

Sensitivity analysis

Results from MD-UKB-BD generally showed greater similarity to PGC MD than to PGC BD. The results of cross-trait meta-analyses may be biased if the power of the composite analyses differ substantially[41,42]. The mean chi-square of MD-UKB (1.7) was greater than that of PGC BD (1.39), suggesting this bias may affect our results (Supplementary Table 2). To examine the extent of this bias, we repeated our analyses using summary statistics for PGC MD that did not include the 23andMe participants nor the UK Biobank participants included in the original study (mean chi-square from meta-analysis with UKB MD = 1.35).

Results

Little evidence of appreciable confounding in meta-analyses

Following each meta-analysis, results were assessed for genome-wide inflation of test statistics using LD Score[27]. The intercept from LD Score regression

was significantly >1 in all cases (1.02-1.06), which has previously been taken as evidence for confounding (for example, by population stratification; Supplementary Table 2). However, inflation of the LD Score intercept can occur in the absence of confounding when assessing large sample sizes[43]. The attenuation ratio from LD Score was < 0.08 in all cases, suggesting that the effect of confounding on GWAS results was minimal (Supplementary Table 2[43]).

Combined MD-UKB-BD meta-analysis

We meta-analysed the PGC MD, PGC BD and the UKB MD cohorts (MD-UKB-BD; cases = 185,285, controls = 439,741, non-overlapping N = 609,424). 73 loci reached genome-wide significance, of which 55 were seen in the depression-only MD-UKB meta-analysis (Table 1; Supplementary Table 3; Supplementary Figures 1 and 2). Hierarchical clustering of the significant loci from both meta-analyses with the same loci from PGC MD, UKB MD, and PGC BD (and the PGC2 SCZ for comparison[21]) resulted in MD-UKB-BD clustering most closely with PGC MD. This indicates that the primary contribution to significant loci in the meta-analysis came from PGC MD rather than PGC BD (Figure 1). Results from UKB MD for these loci clustered closer to PGC BD than to PGC MD, suggesting that the component analyses cluster primarily by their contribution to the meta-analysis, rather than by trait. Despite this similarity between UKB MD and PGC BD when considering genome-wide significant loci, comparisons of the SNP-heritability of the component analyses (Supplementary Table 2) and of the genetic correlations between them (Supplementary Table 4) confirm that UKB MD is more similar in general to PGC MD than to PGC BD. Specifically, the SNP-heritability of UKB MD (13%) is more similar to that of PGC MD (9%) than to that of PGC BD (20%), and the genetic correlation between PGC MD and UKB MD (0.88) is considerably larger than

that between either MD phenotype and PGC BD (both 0.34).

Only five of the 44 PGC MD loci did not reach genome-wide significance in MD-UKB-BD (and all five did reach genome-wide significance in MD-BD2; Supplementary Table 3; Supplementary Figures 1-8). In comparison, only four of the 19 PGC BD loci reached genome-wide significance in the meta-analysis, suggesting that the addition of bipolar cases to depression cohorts enriched for associations with their common phenotypic component, depression.

Of the loci reaching genome-wide significance in MD-UKB-BD, 32 did not reach genome-wide significance in the PGC MD or PGC BD analyses (although all had $p < 1x10^{-5}$ in PGC MD). Although most of these loci have no previous records in the NHGRI-EBI GWAS Catalog, eight have been previously reported in other major depression or major depressive disorder GWAS: loci 27 and 35[16]; locus 30[44]; and loci 42, 44, 49, 51, and 68[41]. Five loci (7, 12, 42, 51 and 68) have previously been associated with schizophrenia[21,45], and there are also multiple reported associations with age at menarche, brain aneurysms, body mass and blood pressure (Supplementary Table 5). A number of these loci contain genes of interest to mood disorders, including *DRD2* and *PCLO* (Supplementary Table 5[44,46,47]).

Gene-wise association analyses in MAGMA identified 361 genes associated with the MD-UKB-BD phenotype at $p < 2.6x10^{-6}$ (Supplementary Table 6). Associated genes were distributed across 120 loci, including 47 of the loci identified in MD-UKB-BD. However, proximity is only a weak indication of the association of a gene with a trait[48]. More evidence is provided by the convergence of brain-derived eQTL and chromatin contact data from a locus onto a single gene (Supplementary Figures 9-28). In MD-UKB-BD, such evidence suggested significant loci may act on *NEGR1* (loci 2 and 3), *RSRC1* (locus 14), *TMEM161B* (18), *LHX2* (41), *SOX5* (53),

LACC1 (56), *PCDH8* (57) and *ZC2HC1C* (61). However, diverse eQTL and chromatin contacts were observed at many of these loci, suggesting these associations may act through other genes as well.

SNP-heritability and genetic correlations

The estimate of SNP-heritability for MD-UKB-BD (8.8% with population prevalence 16%) was more similar to PGC MD (9%) than to PGC BD (17-23%)[11,12]. Significant genetic correlations between MD-UKB-BD and other traits included psychiatric and behavioural, reproductive, cardiometabolic, and sociodemographic traits (Figure 2, Supplementary Table 7). Genetic correlations across psychiatric and behavioural traits are common to psychiatric traits in general[13,49]. One area of difference between the genetic correlations of PGC MD and PGC BD is the genetic correlation with educational attainment, which was negative in PGC MD, but positive in PGC BD. The genetic correlation (r_g) between MD-UKB-BD and educational attainment was -0.058 ($p = 0.004$), intermediate between the results of PGC MD and of PGC BD. Notably, the genetic correlation with intelligence was not significant in either PGC MD and PGC BD, a finding that was also true (following multiple-testing correction) in MD-UKB-BD ($r_g = -0.05$; $p = 0.04$).

Relationship between mood disorder subtypes

Analyses were performed using GWAS data from subtypes of PGC BD (BD1, BD2, SAB) and UKB MD (rMD, sMD, subMD). SNP-heritability for the subtypes ranged from subMD and sMD (both 8%), through BD2 and rMD (10% and 12% respectively) to BD1 and SAB (22% and 29% respectively; Figure 3a; Supplementary Table 2). In hierarchical clustering of the genetic correlations between the different subtypes, the depression subsets (rMD, sMD) clustered

together along with subMD (r_g = 0.9-0.94; Figure 3b; Supplementary Table 4). However, BD1 and BD2 clustered separately, BD2 clustering more closely to the UKB MD subtypes than to the PGC BD subtypes. This was driven by the greater genetic correlation of BD2 to the UKB MD subtypes (r_g = 0.39-0.68) than to SAB (r_g = 0.22).

Conditional analyses

We carried out analyses of MD-UKB conditioning on PGC BD (MD-UKBcBD). Diminished effects (that is, a shrinkage of the odds ratio towards 1) were observed in 51/63 loci reaching genome-wide significance in MD-UKB, which indicates that most loci significantly associated with MD-UKB have the same direction of effect in PGC BD (Supplementary Table 8). Results from the reverse analysis (PGC BD conditioned on MD-UKB: BDcMD-UKB) supports this conclusion, with 14/19 associated loci from PGC BD showing a diminished effect (Supplementary Table 9).

Secondary analyses on MD-UKBcBD reflect the genetic effect on MD-UKB that is not shared with PGC BD and can be compared informatively with the original results for MD-UKB. Similar informative comparisons can be made between BDcMD-UKB and PGC BD. The SNP-heritability of the conditional analyses showed reduced estimates compared to the respective main analyses (MD-UKBcBD: 7%, MD-UKB: 9%; BDcMD: 17%, PGC BD: 20%; Supplementary Table 2). In contrast, the genetic correlations between the conditional analyses and published traits results were similar to the respective main analyses (Supplementary Tables 7, 10-15). Genetic correlations for MD-UKBcBD mirror those for MD-UKB, except that the magnitude of the genetic correlations with schizophrenia (and related analyses, such as the schizophrenia-bipolar disorder meta-analysis) were significantly diminished

(difference in genetic correlation with European subjects in PGC2 schizophrenia between MD-UKB and MD-UKBcBD, $p = 8x10^{-96}$; Supplementary Table 12)[21,50]. The genetic correlations from BDcMD-UKB were also similar to PGC BD, with significant reductions primarily in traits associated with depression, including tiredness and poor general health, although a significant reduction in the genetic correlation with ADHD was also observed ($p = 2x10^{-3}$; Supplementary Table 15[51–53]).

Results from gene set analysis were generally similar between MD-UKB and PGC BD, and in each of the conditional analyses (Supplementary Tables 16-19). Both MD-UKB and PGC BD were significantly enriched for genes previously implicated in schizophrenia, targets of the RNA splicing proteins *CELF4* and *RBFOX1/RBFOX3*, loss-of-function intolerant (pLI09) genes, and genes with products potentially involved in synaptic processes (Supplementary Tables 16, 18). Similar gene sets were also enriched in one disorder only - for example, *RBFOX2* targets were significantly enriched in MD-UKB, but did not reach this threshold in PGC BD. In contrast, gene sets annotated as mutation-intolerant (constrained and genic intolerance RVIS) were significantly enriched in PGC BD but not MD-UKB. However, there were also gene sets which appeared more strongly associated with one disorder than the other, such as anthropometric and behavioural gene sets in MD-UKB, and transporter complexes in PGC BD. In the conditional analyses, results for MD-UKB and MD-UKBcBD were similar, with significantly associated gene sets falling into broad categories of psychiatrically-associated, neurodevelopmental, and anthropometric gene sets (Supplementary Tables 16 and 17). Fewer gene sets were observed in BDcMD-UKB than in PGC BD, with significant enrichment observed for mutation-intolerant gene sets (Supplementary Tables 18 and 19).

The tissue-specificity enrichment of associated genes differed only minimally between the analyses. All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in PGC BD ($p < 0.002$, Bonferroni correction for 24 regions; Supplementary Table 20). By contrast, level 1 cell-type enrichments differed between MD-UKB and PGC BD, especially when comparing the conditional analyses (Supplementary Table 21). Enrichments for neuroblasts and dopaminergic neurons from adult mice were significant in MD-UKB (and MD-UKBcBD) but not in PGC BD. All cell-types significantly enriched in PGC BD (dopaminergic neuroblasts, dopaminergic, GABAergic and midbrain nucleus neurons from embryonic mice, interneurons, medium spiny neurons, pyramidal cells from the CA1 region of the hippocampus and the somatosensory cortex, serotonergic neurons, and striatal interneurons) were also significantly enriched in MD-UKB, but the rank and strength of enrichment differed between the analyses. This became more apparent when comparing the conditional analyses. In addition to the neuroblasts and adult dopaminergic neurons, embryonic GABAergic neurons remain significantly enriched in MD-UKBcBD and not in BDcMD-UKB. Conversely, both sets of pyramidal cells and the striatal interneurons remain significantly enriched in BDcMD-UKB and not in MD-UKBcBD. These differences were also observed when comparing the more narrowly-defined level 2 cell types (Supplementary Table 22).

Shared and distinct relationships with mood disorders and inferred causality

Bidirectional Mendelian randomisation (MR) was used to investigate previously-described relationships between mood disorder phenotypes (MD-UKB, PGC BD, MD-UKBcBD) and external traits: SCZ, educational attainment (EA), intelligence (IQ), body mass index (BMI) and coronary artery disease (CAD). Additional analyses were performed for BDcMD-UKB, but associations with BDcMD-

UKB as an exposure could not be tested because few significant loci were left following conditioning. Similarly, MR associations with PGC BD should be interpreted cautiously, as there were only 19 loci reaching genome-wide significance in this analysis, several of which are removed as potentially pleiotropic in the analyses below.

Results from MR analyses are shown in Figure 4 (Supplementary Tables 23-26). A positive bidirectional relationship was observed between MD-UKB and PGC BD, and this was lost in conditional analyses. We also observed positive bidirectional relationships between SCZ and both MD-UKB and PGC BD, including in conditional analyses. 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 EA differed between the mood disorders - there was a negative bidirectional relationship between EA and MD-UKB (which remained in MD-UKBcBD), but a positive bidirectional relationship between EA and PGC BD (albeit with only nominal significance from PGC BD to EA). In contrast, no significant relationship was observed between mood phenotypes and IQ. This is consistent with a causal role of education (or correlates of education) on mood disorder, with a weaker reciprocal effect of (correlates of) mood disorder altering the length of education.

A positive association was seen from BMI to MD-UKB (and to MD-UKBcBD), but not from MD-UKB to BMI. In contrast, only a nominally significant negative relationship was seen from PGC BD to BMI. Finally, a positive association from MD-

UKB to CAD was observed; no relationship was observed between CAD and the PGC BD phenotypes.

Sensitivity analysis using down-sampled PGC MD

A sensitivity analysis was performed using PGC MD without 23andMe and without the UK Biobank participants included in the original paper. Results from this analysis are reported in full in the Supplementary Materials. Compared to MD-UKB-BD, the down-sampled analysis (dsMD-UKB-BD) was more similar to PGC BD. However, there remained a greater overall similarity to PGC MD. 19 loci reached genome-wide significance in dsMD-UKB-BD, including nine (20%) of those reported in PGC MD, compared with two (11%) of those reported in PGC BD. The SNP-heritability of dsMD-UKB-BD (11%) was closer to PGC MD (9%) than to PGC BD (20%). A comparison of the genetic correlation of dsMD-UKB-BD with published traits showed a mixed set of results, with some correlations becoming more similar to those with PGC BD (such as schizophrenia: down-sampled r_g = 0.61, MD-UKB r_g = 0.35, PGC BD r_g = 0.7), while others remain more similar to PGC MD (such as ADHD, down-sampled r_g = 0.48, MD-UKB r_g = 0.45, PGC BD r_g = 0.14). Notably, a significant negative genetic correlation with intelligence was observed (down-sampled r_g = -0.13, $p = 4x10^{-7}$). This appears to result from excluding the 23andMe participants from PGC MD (Supplementary Materials).

Discussion

We identified 73 genetic loci by meta-analysing cohorts of major depression and bipolar disorder, including 24 loci not previously reported as associated with mood disorders. In gene-level analyses, 361 genes were associated with the combined phenotypes. Gene set analyses indicate key roles for the targets of RNA

processing proteins, for neurobiological and neurodevelopmental processes, and for genes previously-associated with psychiatric disorders, biological annotations that have been previously reported in multiple psychiatric and behavioural GWAS [11,12,21,54]. Results from the mood disorders meta-analyses are strongly genetically correlated with psychiatric phenotypes, but also showed correlations with reproductive development, general health behaviours, socioeconomic traits, and paternal mortality.

Synthesising results across our analyses, there is a general pattern suggesting that the loci and findings from MD-UKB-BD have more in common with those from MD-UKB than from PGC BD. This could result from the greater power of MD-UKB compared to PGC BD. To test this, we conducted a sensitivity analysis, down-sampling PGC MD so that the downsampled MD-UKB more closely matched the power of PGC BD. The results of this analysis suggest that the difference in power increases the similarity of MD-UKB-BD to the MD results. However, this pattern of similarity remained in dsMD-UKB-BD, suggesting it is not entirely the result of the power difference. An alternative (but not exclusive) explanation is that depressive symptoms are both the unifying feature of the mood disorders and the core feature of major depression. As such, meta-analyses of depression and bipolar cohorts may primarily be analyses of depressive symptoms, and as such researchers interested in the study of depressive symptoms may benefit from combining such cohorts in their analyses, despite the increase in heterogeneity that may be expected by adopting such a strategy.

A further explanation for the greater similarity of MD-UKB-BD to MD could be the presence of BD2 cases in PGC BD (although BD1 cases comprised the majority of the PGC BD cases). This follows from another striking feature of our analyses, the

greater genetic similarity of the BD2 cohort (compared to the BD1 cohort) to subsets of UKB MD. In this, we build on evidence from PGC BD, which noted that polygenic risk scores from PGC MD partially distinguish individuals with BD2 from those with BD1[12]. This further supports the integration of individuals with BD2 in the study of depressive symptoms. Furthermore, this reinforces the idea of a genetic mood disorder spectrum, extending from BD1 (with greater genetic similarity to SCZ [12]) through BD2 to MD [1]. Potentially this could extend to the subtypes of MD, with our heritability analyses suggesting rMD may be more similar to PGC BD subtypes than is sMD. This is also supported by analyses included in the Supplementary Materials, which showed polygenic risk scores derived from PGC BD were significantly higher in rMD compared to sMD cases. However, this difference in depression case types requires independent replication, ideally in clinically-defined cohorts.

Our results highlight several differences between the genetics of major depression and bipolar disorder, and this is particularly illustrated in the relationship between each phenotype and EA[55]. The positive genetic correlation between EA and PGC BD, and the negative correlation between EA and MD-UKB, are accompanied by the lack of genetic correlation of either disorder with IQ. This stands in contrast to schizophrenia, which is positively genetically correlated with EA, but negatively correlated with IQ[13]. Our Mendelian randomisation analyses are consistent with a bidirectional influence of EA on risk for mood disorders (and vice versa), with different directions of effect in the two mood disorders. These MR results are also consistent with no significant influence of IQ on risk for either MD or PGC BD. Furthermore, our MR analyses of CAD with MD-UKB were relatively well powered and are consistent with depression increasing the risk for CAD. The interpretation of MR results is often difficult, especially in the case of complex traits and when the

ascertainment of cases varies[24,56,57]. This is particularly the case for analyses for which there are relatively few (< 20) variants used as instruments, such as the PGC BD analyses presented, which should be interpreted cautiously in light of this caveat.

A further area of divergence between the MD-UKB and PGC BD results is the enrichment of cell-type specificity for genes associated with each trait. It is noticeable that the cell-types that are more associated with PGC BD (pyramidal neurons and striatal interneurons) are those that were similarly enriched in previous analyses of schizophrenia [35]. Enrichments more apparent in MD-UKB (neuroblasts, adult dopaminergic neurons, embryonic GABAergic neurons) were much weaker in schizophrenia, but were enriched (amongst other cell-types) in analyses of neuroticism[58]. In addition, the association with serotonergic neurons was stronger and had a higher rank in MD-UKB when compared to PGC BD, which is of interest given the use of drugs targeting the serotonergic system in the treatment of depression[59]. Cell-type enrichment analyses are still novel, and caution needs to be taken in interpretation, especially given that the single-cell data used comes from mice[35,60]. Recent examples of cell-type enrichment analyses in psychiatric and behavioural traits indicate traits primarily differ in the degree or rank of enrichment, rather than there being discrete associations between traits and certain cell-types[35,37,58,60,61]. This is further demonstrated by the differences between mood disorders observed herein.

Our results indicate some genetic differences between major depression and bipolar disorder, but it should be noted that we find far more evidence of shared genetics, particularly in terms of the increase in variant discovery, the enrichment of neurobiological gene sets and the strong genetic correlations with other psychiatric disorders, consistent with other observations in psychiatric genetics[11–13,21,49,51,54,62].

Finally, our data are consistent with the existence of a partially genetic mood disorder spectrum and suggest depression as their common symptom.

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Conflicts of Interest

OA Andreassen has received speaker fees from Lundbeck. ATF Beekman is on speaker's bureaus for Lundbeck and GlaxoSmithKline. G Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. G Crawford is a cofounder of Element Genomics. E Domenici was formerly an employee of Hoffmann–La Roche and a consultant to Roche and Pierre-Fabre. J Nurnberger is an investigator for Janssen and was an investigator for Assurex. SA Paciga is an employee of Pfizer. JA Quiroz was formerly an employee of Hoffmann–La Roche. S Steinberg, H Stefansson, K Stefansson and TE Thorgeirsson are employed by deCODE Genetics/Amgen. PF Sullivan reports the following potentially competing financial interests. Current: Lundbeck (advisory committee, grant recipient). Past three years: Pfizer (scientific advisory board), Element Genomics (consultation fee), and Roche (speaker reimbursement). AH Young has given paid lectures and is on advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Livanova. AH Young is Lead Investigator for Embolden Study (Astrazenaca), BCI Neuroplasticity study and Aripiprazole Mania Study, which are investigator-initiated studies from Astrazenaca, Eli Lilly, Lundbeck, and Wyeth. All other authors declare no financial interests or potential conflicts of interest.

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Figure Legends

Figure 1: Hierarchical clustering of the significant loci from the main meta-analysis (MD-UKB-BD) and the depression-only analysis (MD-UKB) with the same loci from the major depression cohorts (PGC MD and UKB MD), the bipolar disorder cohort (PGC BD), and schizophrenia (SCZ). Blue = positive direction of effect. Red = negative direction of effect.

Figure 2: Selected genetic correlations of previous-reported a) psychiatric traits and b) other traits with the main meta-analysis (MD-UKB-BD), the depression-only analysis (MD-UKB), and the major depression and bipolar disorder analyses before and after conditioning (MD-UKB, MD-UKBcBD, PGC BD, and BDcMD-UKB). Full genetic correlation results are provided in Supplementary Tables 7, 10-12.

Figure 3a: SNP-heritability estimates for the subtypes of bipolar disorder and subtypes of major depression from the UK Biobank. Points = SNP-heritability estimates. Lines - 95% confidence intervals. Full SNP-heritability results are provided in Supplementary Table 2.

Figure 3b: Hierarchical clustering of the genetic correlations between major depression subtypes from UK Biobank (rMD, sMD, subMD) and bipolar disorder subtypes (BD1, BD2, SAB). Blue = positive genetic correlation. Red = negative genetic correlation. Full genetic correlation results are provided in Supplementary Table 4.

Figure 4: GSMR results from analyses with the main meta-analysis (a: MD-UKB-BD), and the major depression and bipolar disorder analyses before and after conditioning (b: MD-UKB; c: MD-UKBcBD; d: PGC BD; e: BDcMD-UKB). Exposures are MD-UKB, PGC BD, intelligence (IQ), educational attainment (EA), coronary artery disease (CAD), body mass index (BMI), and schizophrenia (SCZ).

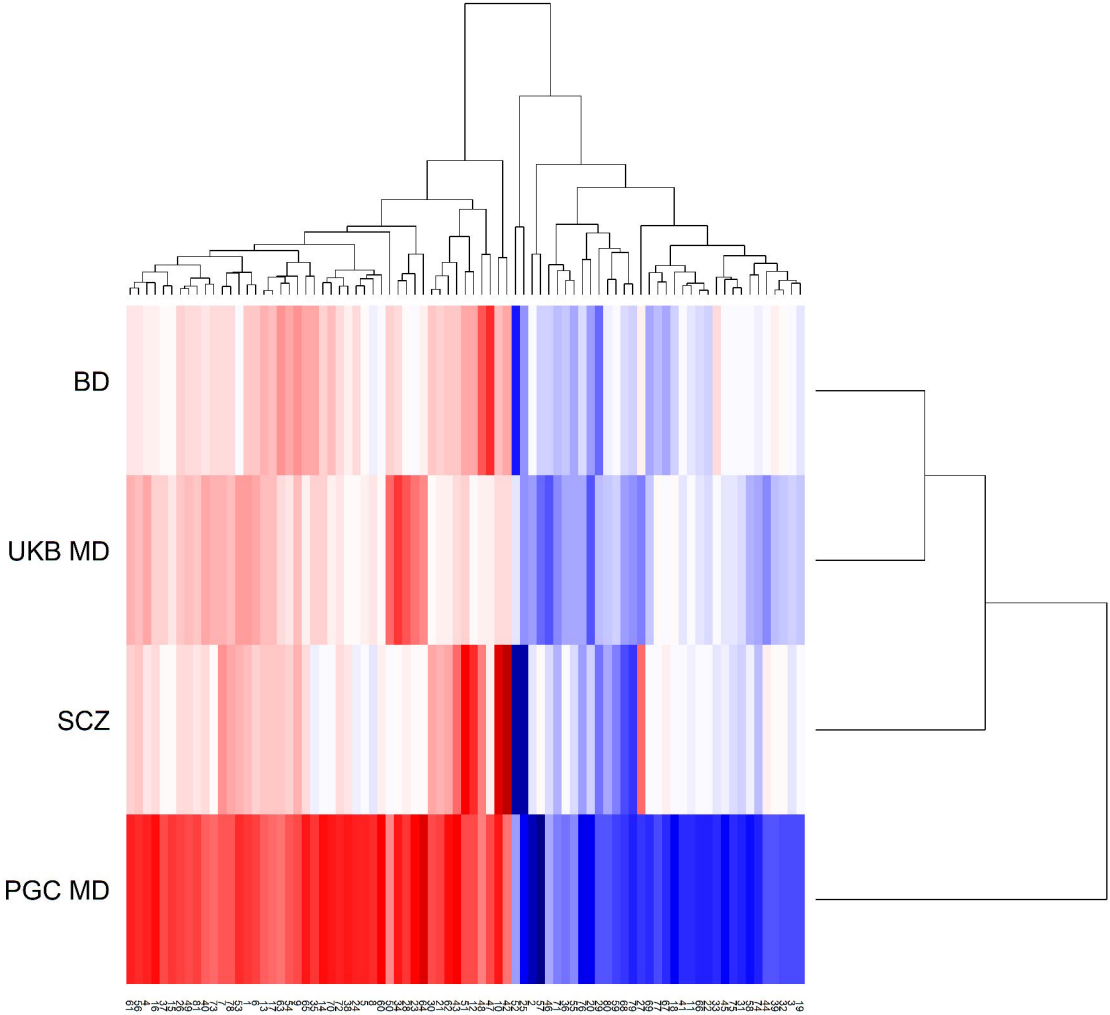
Tables

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p	p min MD-UKB	p min PGC BD
1	1	37192741	rs1002656	T	C	0.97	0.005	$2.71x10^{-11}$	$4.72x10^{-10}$	$2.54x10^{-3}$
2	1	72837239	rs7531118	T	C	0.96	0.004	$1.05x10^{-16}$	$3.25x10^{-17}$	$2.67x10^{-3}$
4	1	80795989	rs6667297	A	G	0.97	0.005	$5.86x10^{-11}$	$8.80x10^{-11}$	$6.00x10^{-3}$
5	1	90796053	rs4261101	A	G	0.97	0.005	$1.78x10^{-8}$	$1.12x10^{-8}$	$3.66x10^{-2}$
6	1	175913828	rs10913112	T	C	0.97	0.005	$1.46x10^{-10}$	$3.91x10^{-9}$	$2.12x10^{-3}$
7	1	177370033	rs16851203	T	C	0.96	0.007	$2.38x10^{-9}$	$1.07x10^{-8}$	$2.75x10^{-2}$
9	2	22582968	rs61533748	T	C	0.97	0.004	$3.84x10^{-11}$	$5.96x10^{-9}$	$4.10x10^{-6}$
10	2	57987593	rs11682175	T	C	0.97	0.004	$2.18x10^{-11}$	$7.07x10^{-10}$	$5.00x10^{-8}$
11	2	157111313	rs1226412	T	C	1.03	0.005	$1.27x10^{-8}$	$3.39x10^{-8}$	$7.29x10^{-4}$
12	2	198807015	rs1518367	A	T	0.97	0.005	$1.18x10^{-8}$	$7.96x10^{-7}$	$4.91x10^{-5}$
13	3	108148557	rs1531188	T	C	0.96	0.006	$1.61x10^{-9}$	$6.74x10^{-8}$	$9.17x10^{-6}$
14	3	158107180	rs7430565	A	G	0.97	0.004	$2.30x10^{-11}$	$2.12x10^{-10}$	$9.41x10^{-4}$
16	4	42047778	rs34215985	C	G	0.97	0.006	$1.72x10^{-10}$	$2.00x10^{-10}$	$9.45x10^{-3}$
17	5	77709430	rs4529173	T	C	0.97	0.005	$4.29x10^{-9}$	$1.35x10^{-7}$	$3.98x10^{-4}$
18	5	88002653	rs447801	T	C	1.03	0.004	$2.29x10^{-10}$	$1.87x10^{-10}$	$8.73x10^{-4}$
19	5	92995013	rs71639293	A	G	1.03	0.005	$5.85x10^{-9}$	$2.34x10^{-8}$	$2.20x10^{-4}$
20	5	103904226	rs12658032	A	G	1.04	0.005	$2.19x10^{-16}$	$6.12x10^{-14}$	$5.19x10^{-6}$
21	5	106603482	rs55993664	A	C	0.97	0.006	$1.87x10^{-8}$	$2.21x10^{-7}$	$2.49x10^{-3}$
22	5	124251883	rs116755193	T	C	0.97	0.005	$1.47x10^{-10}$	$1.33x10^{-9}$	$9.55x10^{-3}$
23	5	164523472	rs11135349	A	C	0.97	0.004	$2.96x10^{-11}$	$1.54x10^{-12}$	$1.48x10^{-2}$
24	5	166992078	rs4869056	A	G	0.97	0.005	$5.21x10^{-9}$	$2.08x10^{-8}$	$5.41x10^{-3}$
25	6	28673998	rs145410455	A	G	0.94	0.007	$7.17x10^{-18}$	$5.06x10^{-15}$	$2.94x10^{-6}$
27	6	101339400	rs7771570	T	C	0.97	0.004	$9.68x10^{-10}$	$4.74x10^{-9}$	$2.17x10^{-4}$
28	6	105365891	rs1933802	C	G	0.98	0.004	$1.05x10^{-8}$	$2.75x10^{-10}$	$4.42x10^{-2}$
29	7	12267221	rs4721057	A	G	0.97	0.004	$7.31x10^{-11}$	$4.79x10^{-11}$	$9.31x10^{-3}$
30	7	24826589	rs79879286	C	G	1.04	0.006	$1.97x10^{-11}$	$1.77x10^{-8}$	$2.70x10^{-8}$
31	7	82514089	rs34866621	T	C	1.03	0.005	$2.21x10^{-8}$	$7.06x10^{-8}$	$4.78x10^{-5}$
32	7	109099919	rs58104186	A	G	1.03	0.004	$7.12x10^{-9}$	$1.34x10^{-9}$	$2.02x10^{-3}$
36	9	11379630	rs10959753	T	C	0.96	0.005	$1.45x10^{-13}$	$6.56x10^{-13}$	$2.14x10^{-4}$

37	9	37207269	rs4526442	T	C	0.96	0.006	$7.97x10^{-11}$	$8.00x10^{-9}$	$5.23x10^{-6}$
38	9	81413414	rs11137850	A	G	1.03	0.005	$1.25x10^{-8}$	$2.53x10^{-7}$	$2.70x10^{-3}$
40	9	119733380	rs10759881	A	C	1.03	0.005	$8.56x10^{-9}$	$1.56x10^{-8}$	$4.15x10^{-3}$
42	9	122664468	rs10818400	T	G	0.98	0.004	$1.29x10^{-8}$	$4.86x10^{-8}$	$6.47x10^{-2}$
43	9	126682068	rs7029033	T	C	1.04	0.008	$2.61x10^{-8}$	$1.89x10^{-8}$	$1.69x10^{-2}$
44	10	104684544	rs78821730	A	G	0.96	0.007	$2.95x10^{-8}$	$1.63x10^{-6}$	$5.63x10^{-6}$
45	10	106563924	rs61867293	T	C	0.96	0.005	$5.64x10^{-12}$	$1.58x10^{-10}$	$1.71x10^{-3}$
46	11	16293680	rs977509	T	C	0.97	0.005	$1.19x10^{-8}$	$3.32x10^{-9}$	$4.48x10^{-2}$
47	11	31850105	rs1806153	T	G	1.03	0.005	$2.81x10^{-9}$	$4.89x10^{-10}$	$4.98x10^{-3}$
48	11	32765866	rs143864773	T	C	1.04	0.008	$1.70x10^{-8}$	$1.40x10^{-7}$	$4.38x10^{-3}$
49	11	61557803	rs102275	T	C	0.97	0.005	$5.04x10^{-11}$	$1.72x10^{-7}$	$1.17x10^{-8}$
50	11	63632673	rs10792422	T	G	0.98	0.004	$2.18x10^{-8}$	$1.26x10^{-5}$	$5.09x10^{-7}$
51	11	88743208	rs4753209	A	T	0.97	0.004	$4.15x10^{-9}$	$1.84x10^{-8}$	$1.17x10^{-4}$
52	11	99268617	rs1504721	A	C	0.98	0.004	$2.24x10^{-8}$	$2.01x10^{-7}$	$1.57x10^{-3}$
53	11	113392994	rs2514218	T	C	0.97	0.005	$3.22x10^{-10}$	$3.09x10^{-8}$	$6.96x10^{-4}$
54	12	2344644	rs769087	A	G	1.03	0.005	$3.27x10^{-8}$	$2.93x10^{-6}$	$2.92x10^{-9}$
55	12	23947737	rs4074723	A	C	0.97	0.004	$3.18x10^{-9}$	$3.23x10^{-10}$	$6.44x10^{-4}$
56	12	121186246	rs58235352	A	G	0.95	0.009	$1.64x10^{-10}$	$7.62x10^{-9}$	$1.66x10^{-4}$
57	12	121907336	rs7962128	A	G	1.02	0.004	$3.63x10^{-8}$	$2.56x10^{-6}$	$1.50x10^{-4}$
59	13	44327799	rs4143229	A	C	0.95	0.008	$2.73x10^{-10}$	$5.68x10^{-10}$	$7.74x10^{-4}$
60	13	53625781	rs12552	A	G	1.04	0.004	$1.25x10^{-23}$	$1.09x10^{-22}$	$9.67x10^{-4}$
61	14	42074726	rs61990288	A	G	0.97	0.004	$2.29x10^{-10}$	$5.95x10^{-11}$	$2.12x10^{-2}$
63	14	64686207	rs915057	A	G	0.98	0.004	$1.92x10^{-8}$	$2.87x10^{-9}$	$1.41x10^{-2}$
64	14	75130235	rs1045430	T	G	0.97	0.004	$9.83x10^{-11}$	$3.07x10^{-10}$	$4.36x10^{-3}$
65	14	104017953	rs10149470	A	G	0.97	0.004	$1.15x10^{-10}$	$2.43x10^{-9}$	$6.24x10^{-5}$
66	15	36355868	rs1828385	A	C	0.97	0.004	$1.15x10^{-8}$	$1.41x10^{-6}$	$1.47x10^{-5}$
67	15	37643831	rs8037355	T	C	0.97	0.004	$4.09x10^{-15}$	$3.38x10^{-15}$	$1.62x10^{-2}$
68	16	6310645	rs8063603	A	G	0.97	0.005	$5.36x10^{-11}$	$6.83x10^{-9}$	$1.39x10^{-4}$
69	16	7667332	rs11077206	C	G	1.03	0.004	$5.49x10^{-10}$	$2.73x10^{-9}$	$5.04x10^{-3}$
70	16	13038723	rs12935276	T	G	0.97	0.005	$4.75x10^{-10}$	$1.54x10^{-8}$	$5.53x10^{-5}$
71	16	13750257	rs7403810	T	G	1.03	0.005	$7.52x10^{-11}$	$4.87x10^{-10}$	$5.54x10^{-3}$
72	16	72214276	rs11643192	A	C	1.03	0.004	$1.46x10^{-11}$	$2.01x10^{-9}$	$2.32x10^{-5}$

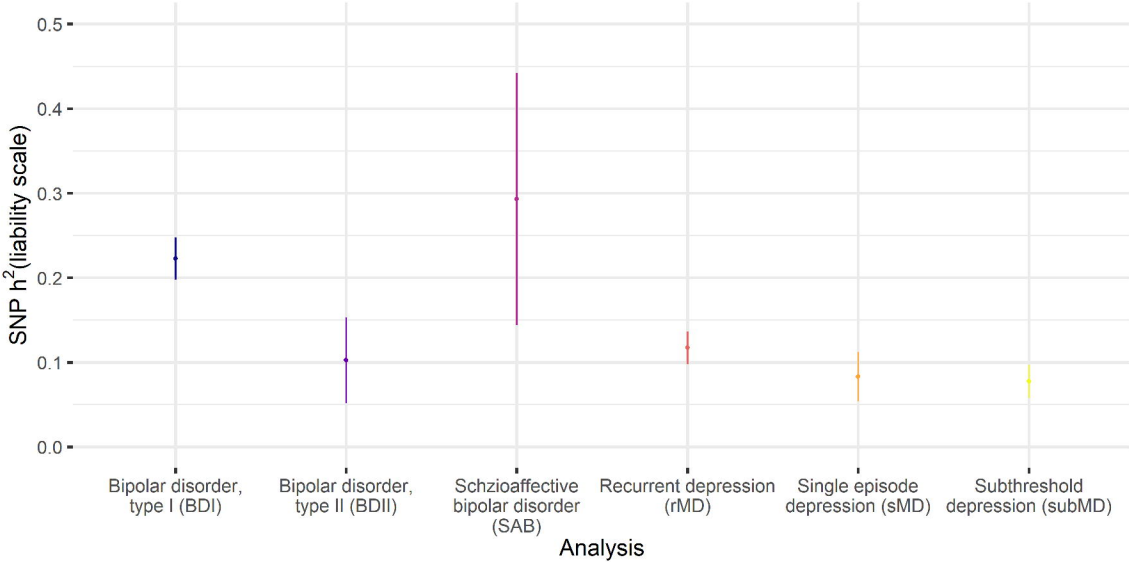
73	17	27363750	rs75581564	A	G	1.04	0.006	$2.47x10^{-10}$	$6.46x10^{-9}$	$2.44x10^{-5}$
74	18	31349072	rs4534926	C	G	1.03	0.004	$9.14x10^{-9}$	$3.43x10^{-7}$	$1.66x10^{-3}$
75	18	36883737	rs62099069	A	T	0.97	0.004	$9.52x10^{-10}$	$4.26x10^{-9}$	$9.91x10^{-5}$
76	18	42260348	rs117763335	T	C	0.97	0.005	$1.33x10^{-8}$	$9.40x10^{-8}$	$1.62x10^{-3}$
77	18	50614732	rs11663393	A	G	1.03	0.004	$1.56x10^{-10}$	$2.44x10^{-10}$	$1.72x10^{-4}$
78	18	52517906	rs1833288	A	G	1.03	0.005	$4.54x10^{-8}$	$9.02x10^{-9}$	$7.98x10^{-3}$
79	18	53101598	rs12958048	A	G	1.04	0.005	$4.86x10^{-14}$	$3.11x10^{-13}$	$2.72x10^{-3}$
80	19	30939989	rs33431	T	C	1.02	0.004	$4.04x10^{-8}$	$1.41x10^{-6}$	$2.84x10^{-3}$
81	20	45841052	rs910187	A	G	0.97	0.005	$3.09x10^{-9}$	$2.56x10^{-8}$	$1.36x10^{-3}$
82	22	41621714	rs2179744	A	G	1.03	0.005	$3.83x10^{-12}$	$3.45x10^{-11}$	$4.69x10^{-9}$
83	22	42815358	rs7288411	A	G	1.03	0.005	$3.86x10^{-8}$	$5.96x10^{-8}$	$4.91x10^{-4}$
84	22	50679436	rs113872034	A	G	0.96	0.006	$1.10x10^{-9}$	$6.13x10^{-9}$	$2.43x10^{-3}$

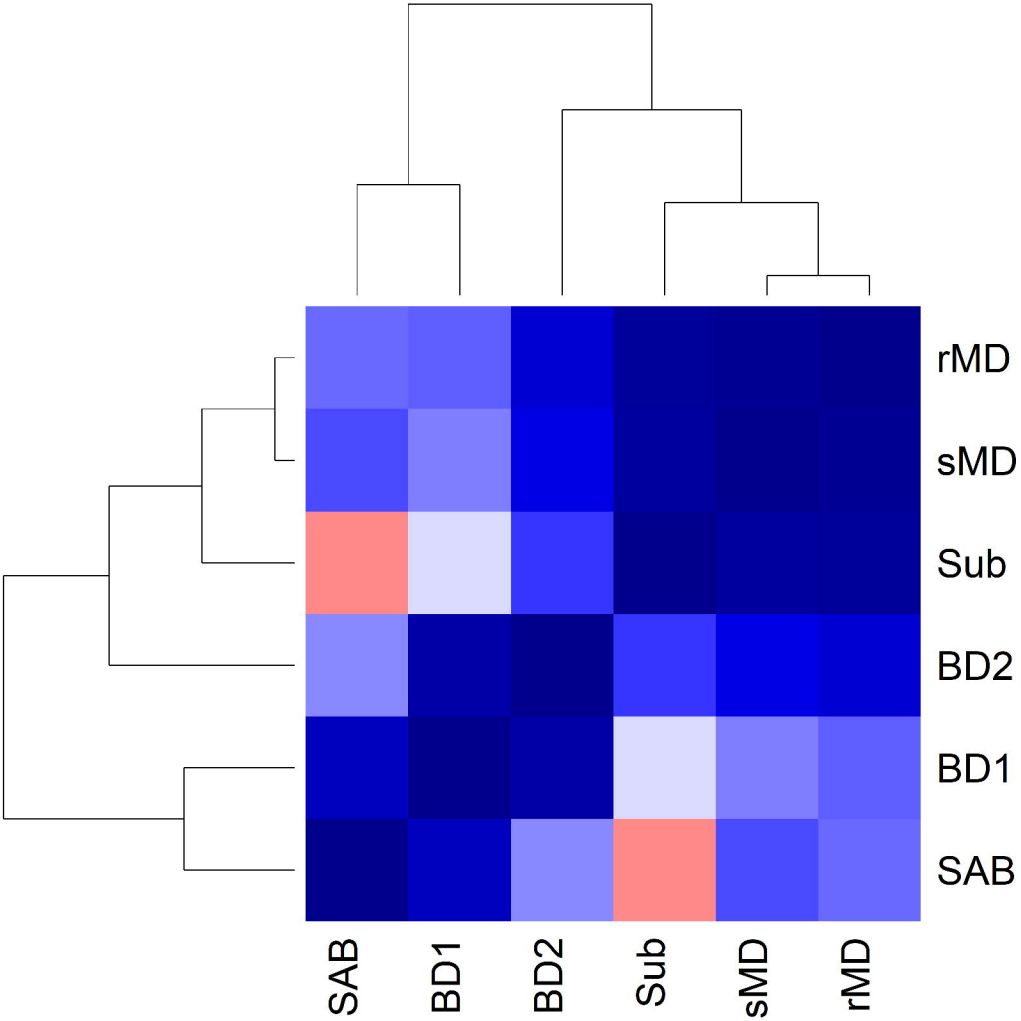
Table 1: Loci genome-wide significant ($p < 5x10^{-8}$) in the MD-UKB-BD meta-analysis. Locus - shared locus number for annotation (Supplementary Table 3); Chr - chromosome; BP - base position; A1 - effect allele; A2 - non-effect allele; p min - minimum p value in that locus for the MD-UKB and PGC BD analyses.

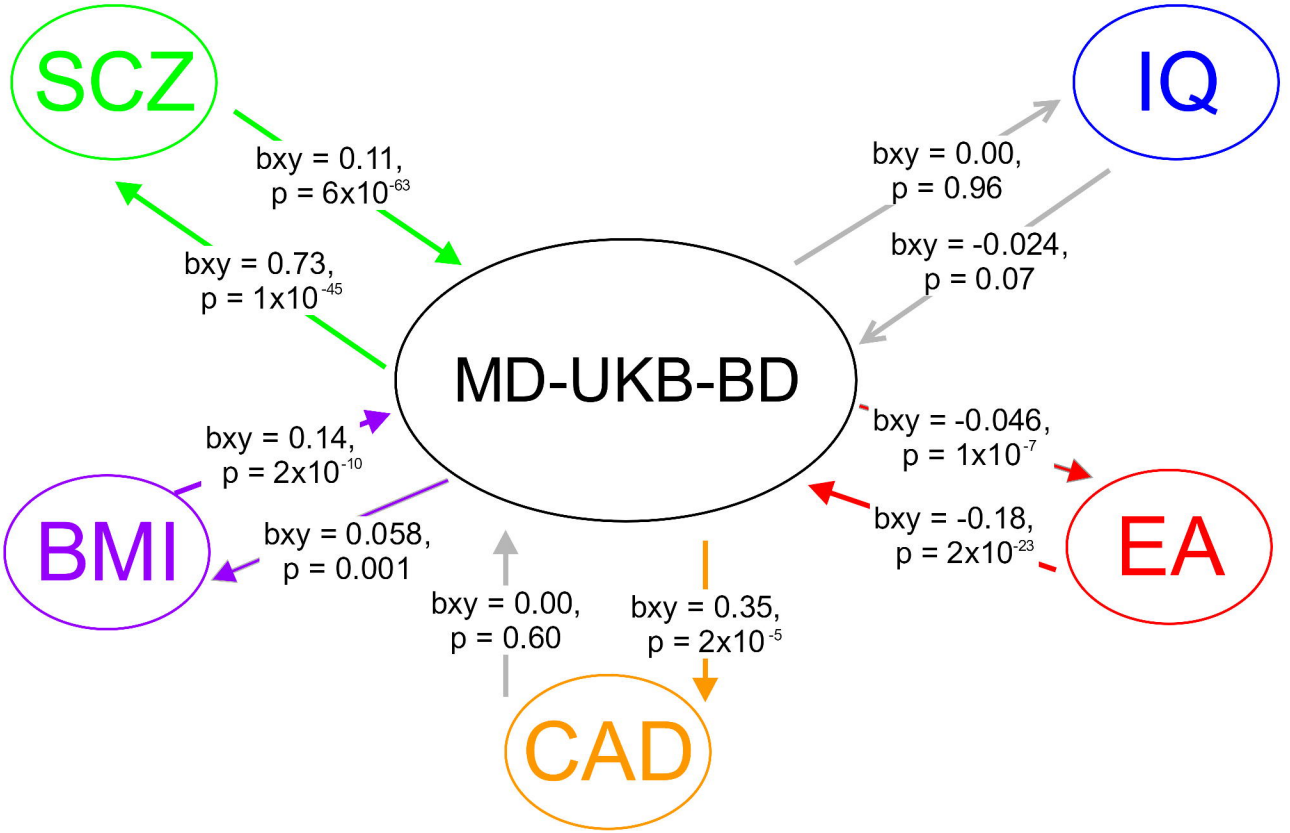

BD
UKB MD
SCZ
PGC MD

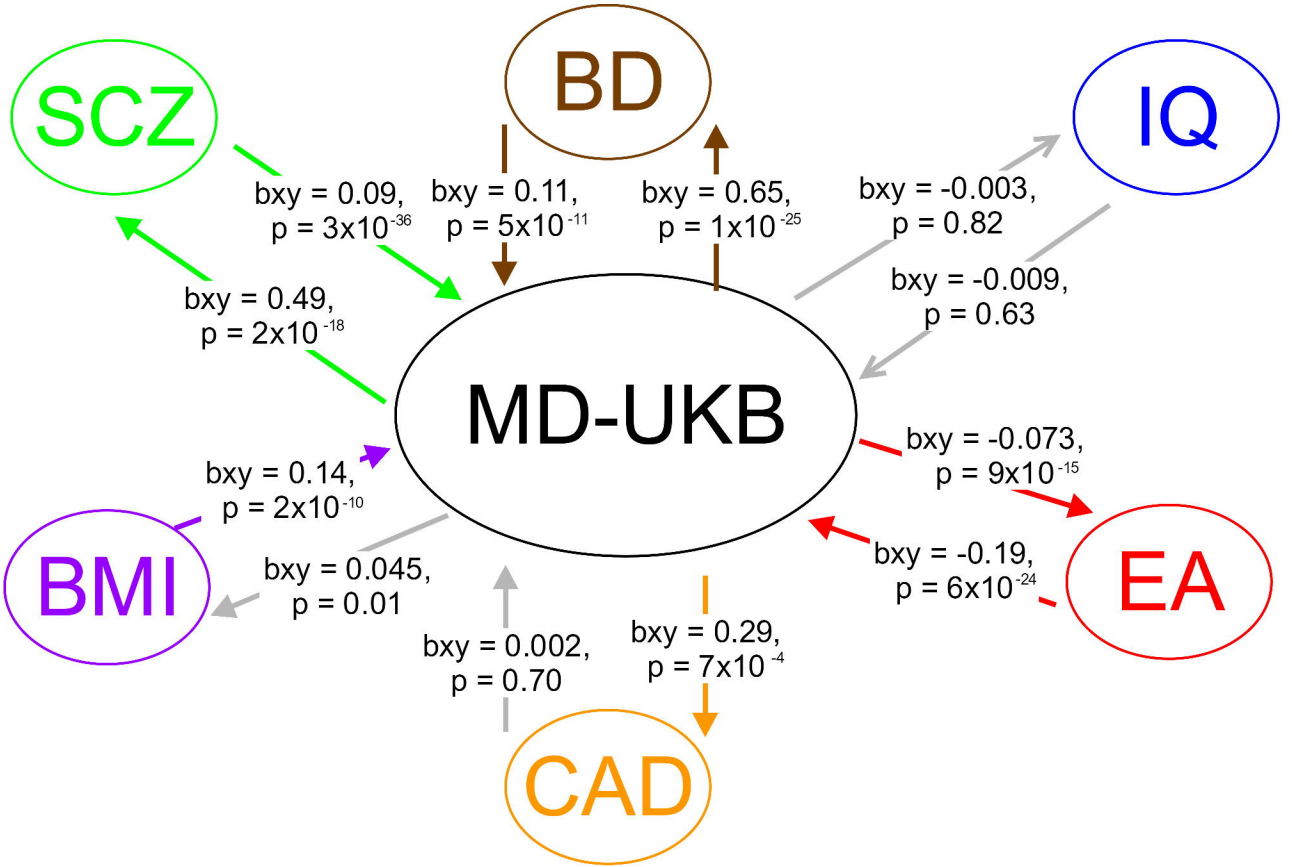
	MD-BD	MD	MDcBD	BD	BDcMD
MD	0.97	1	0.98	0.34	0.09
BD	0.55	0.34	0.14	1	0.96
PGC SCZ EUR (2014)	0.48	0.33	0.19	0.7	0.69
PGC cross-disorder analysis (2013)	0.69	0.52	0.36	0.82	0.8
Lifetime anxieties (UKBB)	0.83	0.84	0.82	0.31	0.11

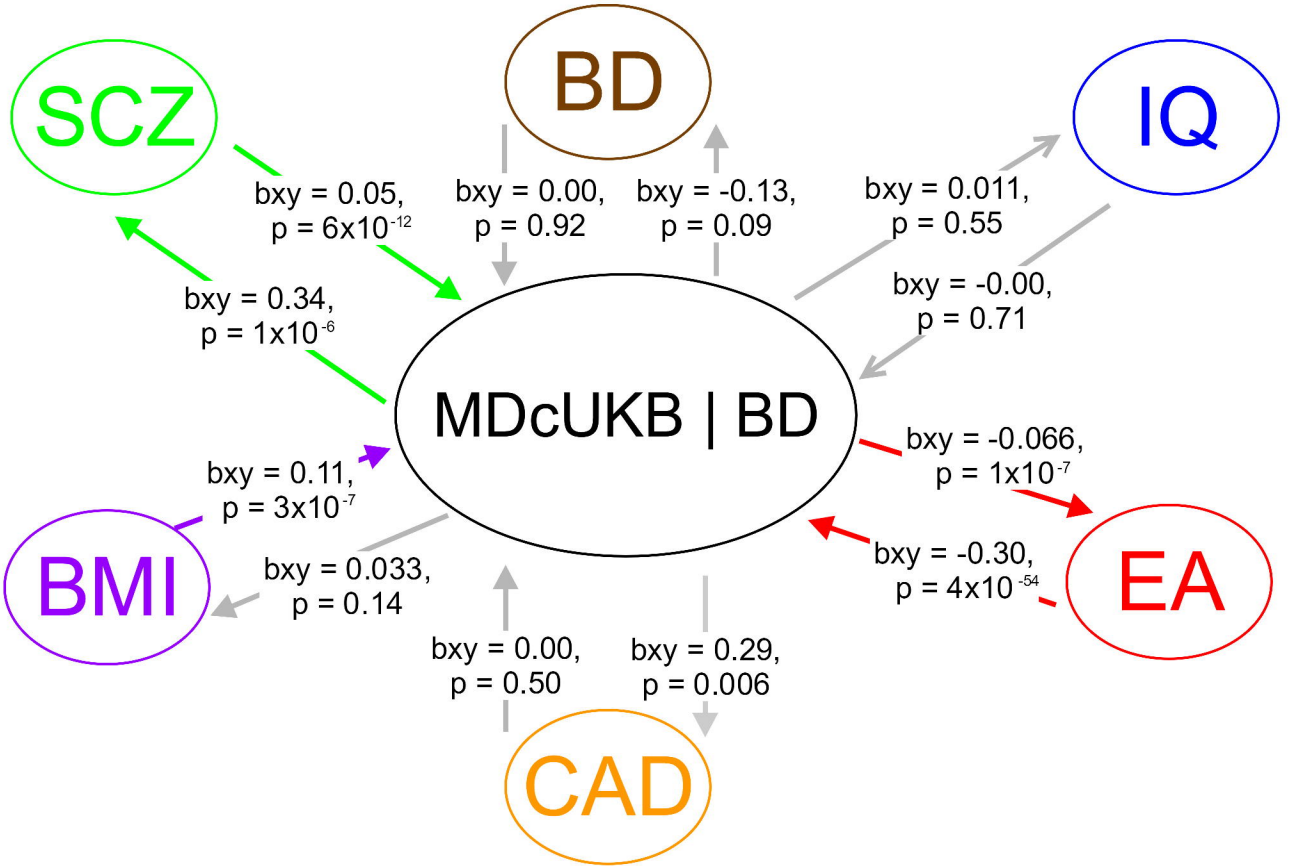
	MD-BD	MD	MDcBD	BD	BDcMD
Insomnia	0.4	0.44	0.44	0.05	-0.06
Years of schooling (2018)	-0.05	-0.1	-0.15	0.19	0.23
Intelligence (2017)	-0.04	-0.03	-0.02	-0.04	-0.04
Coronary artery disease	0.13	0.15	0.17	-0.02	-0.06
Age at first birth	-0.25	-0.27	-0.3	0	0.08
BMI GIANT + UKBB(2018)	0.09	0.13	0.15	-0.06	-0.11
Household income (UKBB)	-0.25	-0.28	-0.32	0.05	0.13

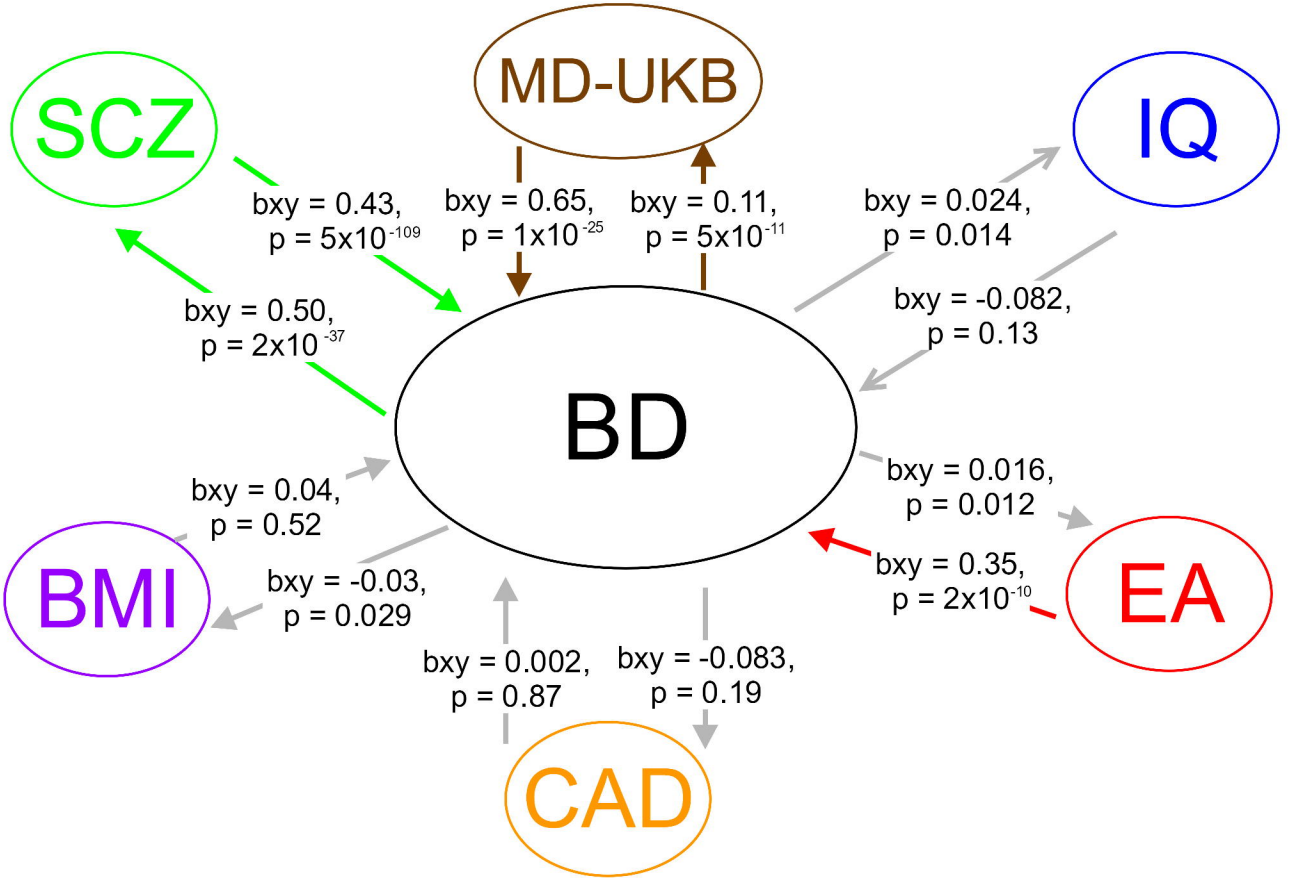

0.5
0.4
0.3
0.2
0.1
0.0
SNP h2(liability scale)
Bipolar disorder, type I (BDI)
Bipolar disorder, type II (BDII)
Schzioaffective bipolar disorder (SAB)
Recurrent depression (rMD)
Single episode depression (sMD)
Subthreshold depression (subMD)
Analysis

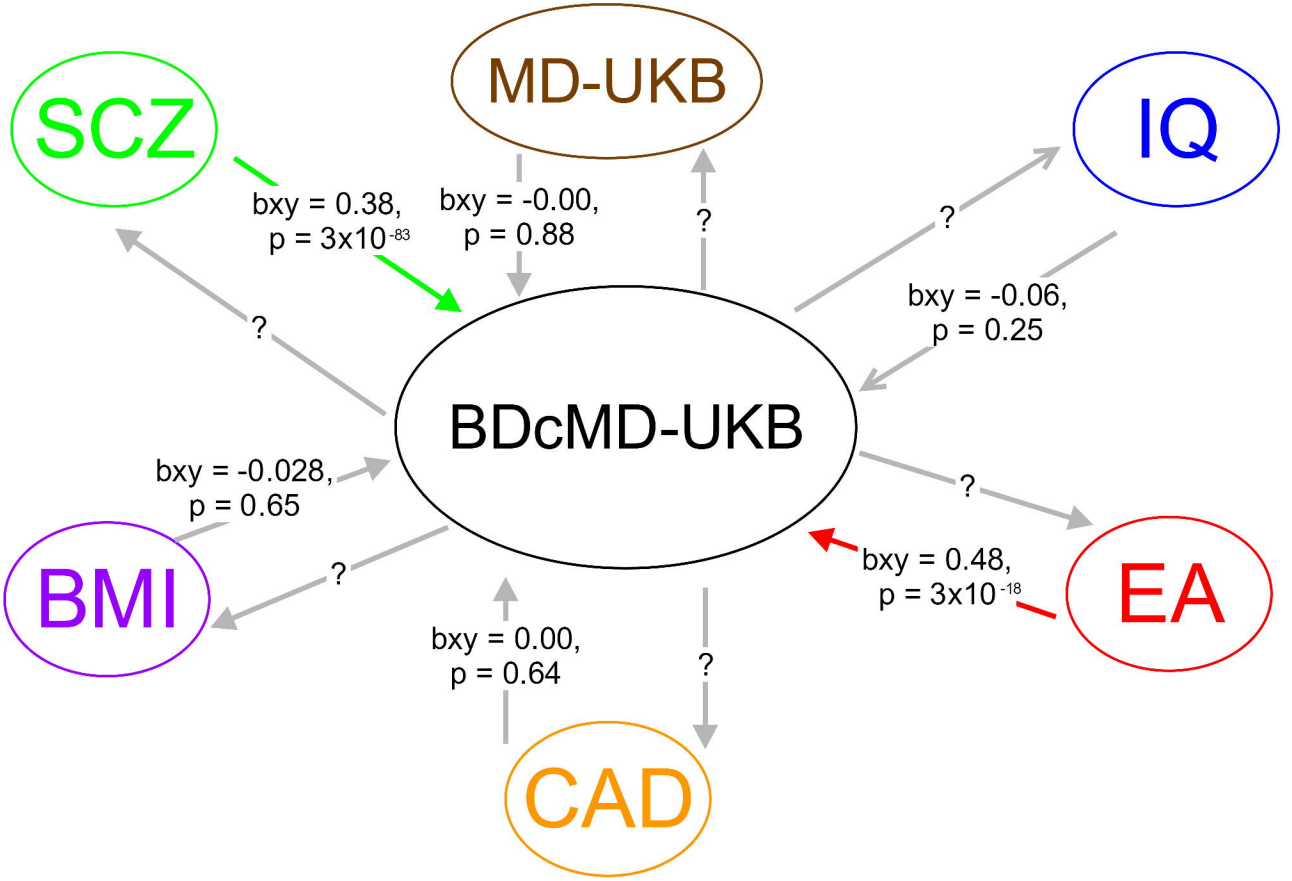

rMD
sMD
Sub
BD2
BD1
SAB
SAB
BD1
BD2
Sub
sMD
rMD


SCZ
IQ
MD-UKB-BD
BMI
EA
CAD
bxy = 0.11,
p = 6x10-63
bxy = 0.73,
p = 1x10-45
bxy = 0.00,
p = 0.96
bxy = -0.024,
p = 0.07
bxy = 0.14,
p = 2x10-10
bxy = 0.058,
p = 0.001
bxy = -0.046,
p = 1x10-7
bxy = -0.18,
p = 2x10-23
bxy = 0.00,
p = 0.60
bxy = 0.35,
p = 2x10-5


SCZ
BD
IQ
MD-UKB
BMI
EA
CAD
bxy = 0.09,
p = 3x10^-36
bxy = 0.11,
p = 5x10^-11
bxy = 0.65,
p = 1x10^-25
bxy = -0.003,
p = 0.82
bxy = -0.009,
p = 0.63
bxy = 0.49,
p = 2x10^-18
bxy = -0.073,
p = 9x10^-15
bxy = 0.14,
p = 2x10^-10
bxy = -0.19,
p = 6x10^-24
bxy = 0.045,
p = 0.01
bxy = 0.002,
p = 0.70
bxy = 0.29,
p = 7x10^-4


SCZ
BD
IQ
MDcUKB | BD
BMI
EA
CAD
bxy = 0.05,
p = 6x10-12
bxy = 0.00,
p = 0.92
bxy = -0.13,
p = 0.09
bxy = 0.011,
p = 0.55
bxy = -0.00,
p = 0.71
bxy = 0.34,
p = 1x10-6
bxy = -0.066,
p = 1x10-7
bxy = 0.11,
p = 3x10-7
bxy = -0.30,
p = 4x10-54
bxy = 0.033,
p = 0.14
bxy = 0.00,
p = 0.50
bxy = 0.29,
p = 0.006


MD-UKB
SCZ
IQ
BD
BMI
EA
CAD
bxy = 0.43,
p = 5x10-109
bxy = 0.65,
p = 1x10-25
bxy = 0.11,
p = 5x10-11
bxy = 0.024,
p = 0.014
bxy = 0.50,
p = 2x10-37
bxy = -0.082,
p = 0.13
bxy = 0.04,
p = 0.52
bxy = 0.016,
p = 0.012
bxy = -0.03,
p = 0.029
bxy = 0.35,
p = 2x10-10
bxy = 0.002,
p = 0.87
bxy = -0.083,
p = 0.19


MD-UKB
SCZ
IQ
bxy = 0.38,
p = 3x10-83
bxy = -0.00,
p = 0.88
?
?
?
bxy = -0.06,
p = 0.25
BDcMD-UKB
bxy = -0.028,
p = 0.65
?
?
BMI
bxy = 0.48,
p = 3x10-18
EA
bxy = 0.00,
p = 0.64
?
CAD