Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Data Selection

In order to find genome-wide association (GWA) summary statistics, we searched the published literature (Pubmed, SCOPUS), data repositories (dbGaP, GWAS ATLAS [https://atlas.ctglab.nl], GWAS catalogue [https://www.ebi.ac.uk/gwas], opentargets.org), and the Psychiatric Genomics Consortium (PGC) website (https://www.med.unc.edu/pgc/). We sought data from studies with the largest available European ancestry, due to the limited availability of well-powered GWA data from other ancestry groups.[1] Most of the selected summary data were produced *via* meta-analyses of large case-control samples by multi-institutional collaborative consortia; detailed descriptions of selection criteria, quality control, and analyses are described within the individual studies (see references in Table 1 and S. Table 1). We included 14 psychiatric phenotypes, including attention deficit hyperactivity disorder (ADHD; *N* = 53,293)[2], anorexia nervosa (AN; *N* = 72,517)[3], bipolar disorder (*N* = 51,710)[4], the PGC cross-disorder phenotype (PGC-CD; *N* = 107,785)[5], cannabis use disorder (CUD; *N* = 357,806)[6], major depressive disorder (MDD; *N* = 500,199)[7], obsessive-compulsive disorder (OCD; *N* = 9,725)[8], opioid use disorder (OUD; *N* = 82,707)[9], problematic alcohol use (PAU; *N* = 435,563)[10], post-traumatic stress disorder (PTSD; *N* = 174,659)[11], schizophrenia (SZ; *N* = 105,318)[12], and Tourette's syndrome (TS; *N* = 14,307).[13] We also included three continuous phenotypes: generalized anxiety disorder (*N* = 175,163)[14] was assessed based on the GAD-2 Score,[15] a 2-item self-report assessment of the frequency of worrying and related physical sensations;[15] the personality trait of neuroticism (*N* = 168,105);[16] and another dispositional trait reflecting risk tolerance (RT; *N* = 315,894).[17] We selected 13 immune-related phenotypes, including allergic rhinitis (AR; *N* = 289,307),[18] asthma (*N* = 385,822),[18] atopic dermatitis (AD; *N* = 40,835),[19] celiac disease (*N* = 15,283),[20] Crohn's disease (*N* = 40,266),[21] hypothyroidism (HYPO; *N* = 244,890; primarily autoimmune-mediated in developed countries),[18] primary biliary cholangitis (PBC; *N* = 13,239),[22] primary sclerosing cholangitis (PSC; *N* = 14,890),[23] rheumatoid arthritis (RA; *N* = 58,284),[24] systemic lupus erythematosus (SLE; *N* = 23,210),[25] type 1 diabetes (T1D; *N* = 26,890),[26] ulcerative

colitis (UC; *N* = 45,975),[21] and vitiligo (*N* = 44,266).[27] Data for multiple sclerosis could not be shared at the time of our search.

We searched the literature using the following SCOPUS for articles identifying risk factors for psychiatric, allergic, autoimmune, and inflammatory disorders. We identified numerous risk factors that influence liability to both psychiatric and immune-related disorders, including age,[28,29] sex,[30,31] alcohol and tobacco consumption,[32–37] cognitive processing,[38] diet,[39–42] exercise,[43,44] early life stress or trauma,[45–48], educational attainment,[49] infection and microbial dysbiosis,[50–53] perinatal factors,[54–59] obesity,[60,61] sleep,[62,63] socioeconomic status and neighborhood deprivation,[64–67] social connectedness,[68] and toxic exposures.[69,70] Additionally, our review identified considerable evidence that chronic stress leads to dysregulation of autonomic and neuroendocrine signaling mechanisms, which can have direct effects on liability to psychiatric and immune-related disorders, but are additionally proposed to exert effects through changes in function of certain immune cell populations, chronic low-grade inflammation, gastrointestinal dysbiosis, and changes in gastrointestinal and vascular permitaiblity.[71–75] As such, we sought to include phenotypes that capture aspects of the human stress response. We included resting heart rate,[18] heart rate reactivity and recovery during exercise,[76] and heart rate variability,[76] all of which are influenced by cardiac autonomic signaling. We sought well-powered GWA data relevant to these phenotypes and ultimately selected 15 phenotypes, including body mass index (BMI; *N* = 806,834)[77], cigarettes per day (CPD; *N* = 263,954)[78], cognitive processing (CP; *N* = 257,828)[79], alcoholic drinks per week (DPW; *N* = 537,349)[78], educational attainment (EA; *N* = 766,345)[79], the frequency of moderate-intensity exercise (EXER; *N* = 367,908)[18], annual income (*N* = 332,594)[18], sleep duration (*N* = 446,118)[80], social deprivation (*via* the Townsend Index;[81] SOCD; *N* = 420,035),[82] and the frequency of social interactions (SOCI; *N* = 383,941).[18] We also selected phenotypes that capture aspects of the human autonomic response to stress, including resting heart rate (HR; *N* = 361,411),[18] HR increase during and recovery after exercise (HRI and HRR; *N* = 58,818),[83] heart rate variability (HRV; *N* = 28,122).[83] We sought to include cortisol-related phenotypes, [84,85] but this was precluded by low heritability (h^2) *Z*-statistics and relatively small sample size. In order to restrict the scope of the study and preserve statistical power, we made the somewhat arbitrary decision to exclude a number of well-powered GWA studies capturing a variety of dietary consumption phenotypes,[86,87] and we also did not examine studies of gut microbiome composition and related metabolites.[88,89] The final list of phenotypes is provided in S. Table 1.

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Genetic Correlations *via* LD-Score Regression

We removed SNPs with MAF < 1% based on the 1000 Genomes Phase reference panel for European populations and we excluded the major histocompatibility region. We used *LD-score regression* (LDSC)[90] with default settings and the HapMap3 reference panel to estimate SNP h^2.

Mendelian Randomization

We briefly review the assumptions and limitations of MR: 1) The instrument SNPs are associated and have a causal effect on the exposure phenotype. For exposures with sparse genetic architecture, weak associations between instrument SNP and exposure are likely to bias toward null findings. For polygenic phenotypes, the inclusion of a larger set of lower confidence instrument SNPs could increase the likelihood of selecting instrument SNPs that have a pleiotropic mechanism relevant to both the exposure and outcome phenotype. One approach to cope with potential bias introduced by weak instruments and highly polygenic phenotypes is to perform MR with robust associated profile scores.[91] 2) The exposure phenotype should share no common cause with the outcome phenotype (*i.e.,* there are no confounding factors). When this possibility is not excluded, multivariable MR can be used to reassess exposure-outcome relationships while adjusting for genetic associations of a third variable. 3) The instrument SNPs only exert effects on the outcome phenotype through the exposure phenotype, as opposed to shared biological mechanisms or mediation through some other phenotype. Outlier removal, heterogeneity testing, sensitivity analyses, and comparison across multiple MR methods can help evaluate this assumption. 4) Two-sample MR rests on the assumption of independent samples drawn from the same population and sample overlap can bias toward rejecting the null hypothesis, especially when there are weak instruments with overestimated effect sizes.

For the present study, the *TwoSampleMR* (TSMR)[92] package was used to harmonize data and threshold and clump instrument SNPs ($p_1 < 5\text{x}10^{-8}$, $p_2 < 0.001$, window = $1\text{x}10^5$). For phenotypes denoted with † in Table 1, this identified < 15 LD-independent SNPs, so we instead used a suggestive threshold of $p < 1\text{x}10^{-5}$. Bidirectional MR analyses were performed using inverse variance-weighted (IVW) method with significance set at FDR $q < 0.05$ and we verified findings with Egger-based models (reported in S. Tables). We performed single-SNP, heterogeneity, and leave-one-out (LOO) sensitivity analyses. We verified effects with the *mr.raps* package,[91] which uses adjusted profile scores that are more robust to outliers in the genetic instrument and

estimates effects under assumptions of pervasive balanced pleiotropy, which can account for weak instrument bias. We preferentially report results after removal of potential outlier SNPs (|standardized residual| > 2.5 *s.d.* of the mean). We assessed the effects of adjustment for each of the third variables separately using the *MVMR* package with default settings.[93] To check for possible sample overlap among the MR effects, we examined LDSC covariance intercepts. For those with significant positive values, we repeated bidirectional IVW analyses using the *MRlap* package (default settings) to adjust for additional bias introduced by sample overlap.[94]

Characterization of Loci

For six phenotype pairs with robust MR effects (*i.e.,* FDR $q < 0.05$ and consistent across sensitivity and MVMR-adjusted analyses), a two-sided meta-analysis was performed using the ASSETT package.[95] Because we encountered an unresolvable error when combining continuous and dichotomous phenotypes, the effect of RT on AR was not assessed. SNPs showing significant effects for only one of the phenotypes were removed from the analysis. Subsets of SNPs with concordant and discordant effects were separately advanced for enrichment analysis using FUMA's SNP2GENE function. The concordant subsets included information about the direction of the effects, while the latter subsets contained only the overall model p-values. FUMA analysis was performed with clumping setting of $r^2 < 0.1$, *p*-value thresholds corresponding to the threshold used to define the MR instrument (*i.e.,* $5x10^{-8}$ and in some cases $1x10^{-5}$) and the second threshold of 0.05, with the window size of 250kB, using the default settings for both positional and eQTL-based gene mapping. For cell-type analysis, we included available human single-cell RNA-seq reference datasets.[96–105] For cell types surviving multiple test correction (family-wise FDR $q < 0.05$), we examined the pair-wise conditional analyses within- (*i.e.* Step 2) and across-reference datasets (*i.e.* Step 3) to prioritize among potentially correlated cell types. High proportional significance (PS; *i.e.*, ≥ 0.8) indicates complete independence, while lower values suggest partial or complete dependence on other correlated cell types. In S. Figure 5B, the numeral *2* denotes a cell type with ≥ 0.8 in Step 2, while 2' denotes the cell type with the highest PS despite being < 0.8. A similar relationship applies between numerals 3 and 3' with respect to Step 3 conditioning PS.

eDiscussion

The main findings of our study supported modest positive effects of psychiatric on immune liability, where the relevant loci were primarily enriched with brain tissues and cell types, but also contained signals for

peripheral leukocytes and lymphoid tissue. These loci were also enriched in signal for various behavioral traits, immune cell counts, and biological terms including cell adhesion, calcium-binding, and response to viral infection. Below, we provide a literature search of individual genes implicating these biological terms. When we considered the six robust positive MR effects (*i.e.,* FDR $q < 0.05$ and consistent across sensitivity and MVMR-adjusted analyses), 54 psychiatric instrument loci were independent of third variable effects. These were significantly enriched (FDR $q < 0.05$) for several annotations, including cellular adhesion (comprised of genes *ATXN1, ADD3*, and the protocadherin-α family within a locus in 5q31.3; S. Table 5).

For *ATXN1*, the relevant protein participates in complex interactions to regulate transcription and splicing, though its exact roles are not well understood. Our review identified considerable mechanistic evidence linking polyglutamine expansion mutations in this gene (and others) with various neurodegenerative disorders, including spinocerebellar ataxias and amyotrophic lateralsclerosis,[106–108] but its less clear how it may relate to the penetrance of autosomal dominant Alzheimer's phenotypes.[109] This gene was identified in bioinformatic analyses based on enrichmed protein-protein interactions with 19 candidate genes for SZ.[110] Additionally, *ATXN1* appears to have relevance to immune-related diseases, as loss of function is associated with more severe disease in a mouse model of multiple sclerosis, and this was mediated by effects on a potentially pathogenic B-cell subpopulation.[111,112] It plays a role in extracellular matrix remolding during lung development and is down-regulated in a model of asthma.[113,114] Additionally, it was identified in prior pharmacogenetic GWAS of IBD treatment response.[115] GWAS studies support associations of ATXN1 with cognitive function, intelligence, and educational attainment.[116,117]

ADD3 encodes γ-adducins, which are ubiquitously expressed, heteromeric proteins that participate in membrane-associated spectrin-actin cytoskeletal networks and interact with calmodulin.[118] Homozygous loss-of-function mutations within a consanguineous family were associated with inherited cerebral palsy.[112] Loss-of-function mutations have also been associated with renal podocyte dysfunction and related chronic kidney disease.[119] GWAS data suggest this gene may be relatively specific to bipolar disorder[120] and it was identified in an earlier study comparing bipolar I and II.[121] There is literature linking γ-adducins to electrophysiological plasticity induced by environmental stimuli (*e.g.,* effects of cocaine exposure on striatal neurons) and learning behavior (e.g., Morris water maze).[122,123] Another line of research associated gamma-adducin expression with blood pressure homeostasis and with cerebrovascular and blood-brain-barrier dysfunction.[119,124] A GWAS

study in East Asian ancestry identified *ADD3* in association with neonatal biliary atresia.[125] *ADD3* was identified among differentially expressed genes that discriminated intestinal biopsies from Celiac-affected individuals and subsets of first degree relatives that lacked serological evidence of disease activity.[126] Furthermore, ADD3 was down-regulated in a mouse model of spontaneous colitis caused by macrophage-restricted knockout of the *IL10RA* gene.[127] ADD3 was also identified among CD4+ T cell genes whose expression discriminated high- and low-atopy subtypes of asthma and predicted differences in eosinophil counts and IgE levels.[128]

Protocadherins are cell adhesion molecules that undergo alternative splicing and combinatorial heteromerization to allow specificity of cell recognition, though their exact roles in the developing and adult CNS are not well understood yet.[129–131] Multiple subtypes of protocadherins have been identified, and members of the clustered α-protocadherin family have been associated with psychiatric and neurodevelopmental phenotypes.[130] Deletion of this family was associated with reduced post-injury axon outgrowth, myelination, and expression of *BDNF* in rodent model.[132] Deletion of this family also impacted cortical neuron migration[133] and serotonergic fiber development and maturation.[134,135] One study found α-protocadherins were upregulated during stimulation of Th_2 lymphocytes.[136] We also found relevant associations with other types of protocadherins. *PCDH1* plays a well-characterized role in asthma pathophysiology and is important in the response to glucocorticioids.[137,138] Roles in GI epithelial structure and function have been observed for members of the other protocadherin families.[139]

We also saw enrichment for genes involved in calcium-binding (including *LTBP2*, *PLCB2*, and *MATN4*). *LTBP2* encodes a latent transforming growth factor (TGF) beta binding protein, which is found in association with fibrillin in the extracellular matrix and thought to help limit the availability of TGF-β.[140] TGF-β plays a role in regulating inflammation and promoting airway and extracellular matrix remodeling in asthma.[145] Both TGF-β and *LTBP2* genes play roles in inflammation-induced fibrosis in other organs, including the intestines.[146,147] Mutations of *LTBP2* are associated with congenital ophthalmic disorders,[141142] but there is less evidence linking it with psychiatric phenotypes. Research in pulmonary development identifies roles for several members of the LTBP gene family.[143] Secreted protein product of *LTBP2* was identified as a biomarker of idiopathic pulmonary fibrosis.[144] Interestingly, *LTBP2* was identified among genes differentially expressed after antibiotic treatment designed to alter the gut microbiome.[148] Research in oncology identifies a role for *LTBP2* in tumor/metastasis suppression for several malignancies.[149,150] *PLCB2* encodes phospholipase C beta-2, an enzyme that

participates in G-protein-coupled signaling pathways relevant to taste receptors and regulation of platelet response.[151,152] This gene was identified in secondary analyses of SZ GWAS data.[153] It was also found among down-regulated genes in the amygdala of rats subjected to chronic stress.[154] This gene also participates in pathways that influence differentiation, activation, and chemotaxis of multiple immune cells.[155,156] One study identified a role in negative regulation of inflammatory signaling in a model of viral infection.[157] It was also among over-expressed genes in childhood asthma.[158] *MATN4* encodes matrilin-4, a member of the von Willebrand factor A domain-containing protein family, which are involved in formation of filamentous extracellular matrix-associated in various tissues. Mutations in this gene have been found in neurogenetic syndromes within consanguineous families.[159] The gene was also identified among those differentially methylated in children in relation to history of early life adversity and adults in relation to air pollution.[160,161] Matrilin-4 has been shown experimentally to regulate stress-induced hematopoietic stem cell proliferation.[162] *MATN4* was also identified among hundreds of differentially expressed genes identified in IBD.

We also observed enrichment among genes downregulated in a fibroblast model of human cytomegalovirus infection, including *AKT3, ADD3, CHMP2A, TMCO6, REV3L, TRAF3IP2,* and *TNKS. AKT3* encodes a serine/threonine kinase that regulates signaling in response to growth factors like platelet-derived growth factor and insulin-like growth factor 1. In humans, mutations in *AKT3* are associated with profound neurodevelopmental phenotypes[163] and experimental models also suggest roles in behavioral traits.[164–167] In T-regulatory cells, *AKT3* inhibits interferon-γ, and loss of this function may promote loss of this cell population's suppressive function.[168] Loss of function is also associated with more severe phenotypes in models of multiple sclerosis.[169,170] *AKT3* was investigated as a potential susceptibility gene in an association analysis between Danish and Genetics of Asthma International Network families, but associations were non-significant.[171]

CHMP2A encodes a protein that functions within the endosomal sorting systems and within exosomes. Loss of function mutations are thought to contribute to proteostatic stress that causes neurodegenerative phenotypes.[172] *TMCO*6 is a transmembrane protein whose function is not well characterized, but loss-of-function mutations are associated with a subtype of mitochondrial complex I deficiency. Within bipolar-affected and unaffected individuals, this gene was near a locus associated with soluble CD14 levels (a non-specific marker of monocyte activation) within cerebrospinal fluid samples.[173]

REV3L encodes a catalytic subunit of DNA polymerase zeta, which is found in the mitochondria and plays a role in the response to DNA damage. Numerous studies have examined its role in malignancies,[174,175] including cervical cancer,[174] chemoresistant squamous cell carcinoma of the head and neck,[176,177] and non-small cell lung cancer.[178] Defects in this gene are associated with genotoxic stress and interferon activation,[179] and are disruptive to mammalian embryonic development.[180–182] SNPs in intergenic regions including *REV3L* and *TRAF3IP2* were associated with rheumatoid arthritis in a large-scale study of black South Africans.[183]

TRAF3IP2 encodes an adaptor protein that plays a central role in innate immunity response to pathogens, inflammation, and stress via regulating responses of the Rel/NF-kappaB transcription factor family members in their response to cytokines.[184] TRAF3IP2 facilitates pro-inflammatory IL-17 signaling,[185–187] which has been implicated in endothelial dysfunction and cardiovascular disease,[188–191] as well as obesity-related vascular insulin resistance.[192] GWA studies have identified a locus in *TRAF3IP2* with common variants affecting susceptibility to psoriasis and psoriatic arthritis,[194195] as well as an association with cutaneous manifestations of inflammatory bowel disease,[196] and susceptibility to mucocutaneous adverse reactions among patients treated with Nevirapine.[197] TNKS encodes a poly-ADP-ribosyltransferase involved in several processes, including activation of Wnt/beta-catenin signaling pathway,[198,199] as well as in regulating telomere length[200] and vesicle trafficking.[201] It's been studied for its role in malignancy,[202,203] herpesvirus infection,[204,205] and obesity.[206]

Among the 54 loci involved in six robust psychiatric-immune MR effects (described in main text and S. Table 4), we observed nominal enrichment (uncorrected $p < 0.05$) for multiple immunologic signatures (*e.g.,* genes down-regulated by IFN-gamma in microglia, $p = 1.3 \times 10^{-4}$, targets of several transcription factors (*e.g.,* ELK1 $p = 1.5 \times 10^{-4}$; E2A $p = 0.01$; STAT1 $p = 0.01$), and transcripts upregulated by suppression of JAK2 ($p = 0.01$; S. Table 5). Overall, these findings support the idea that genes with pleiotropic effects potentially relevant to both psychiatric and immune-related disorders were identified in association with some of the loci contributing to significant MR effects.

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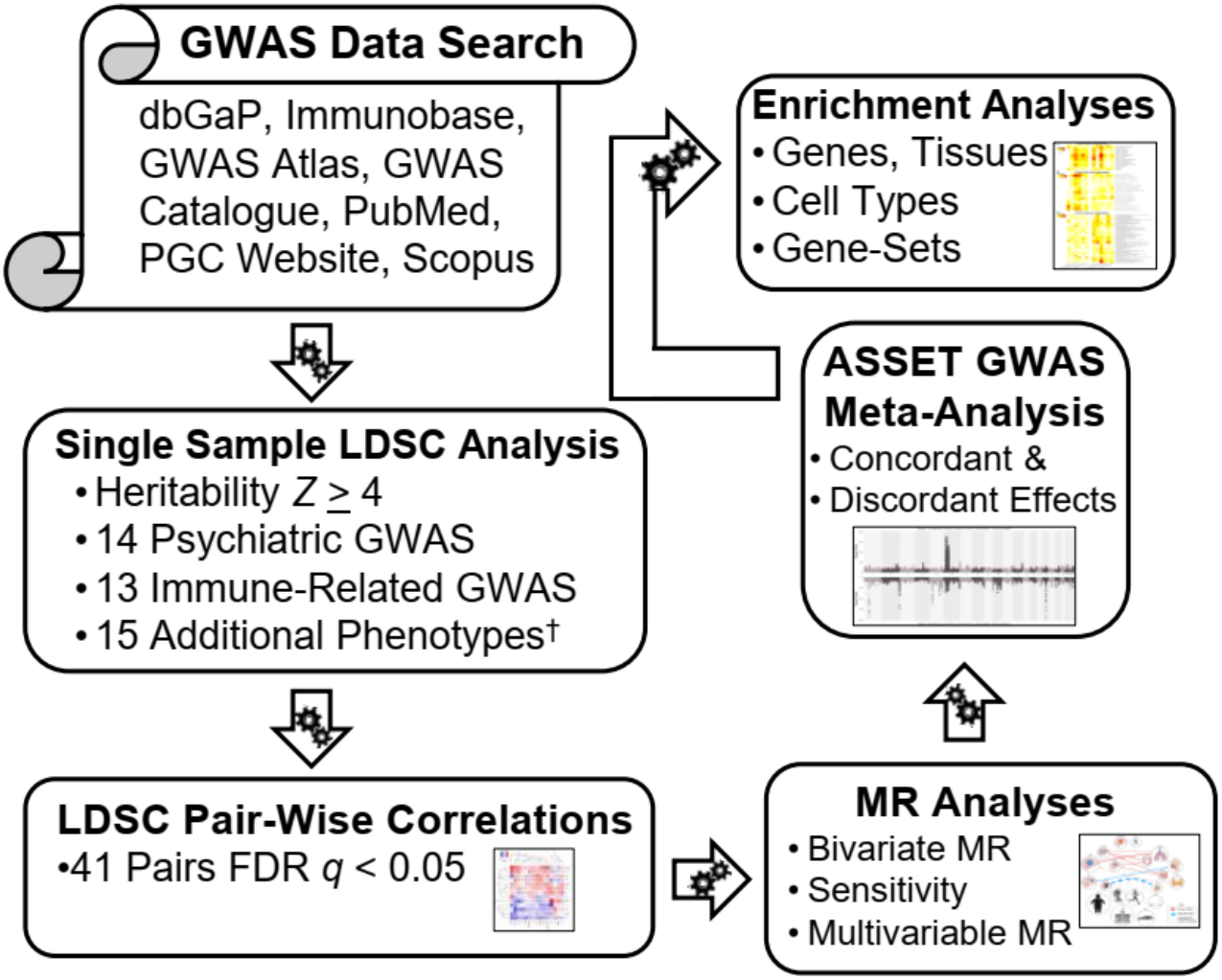
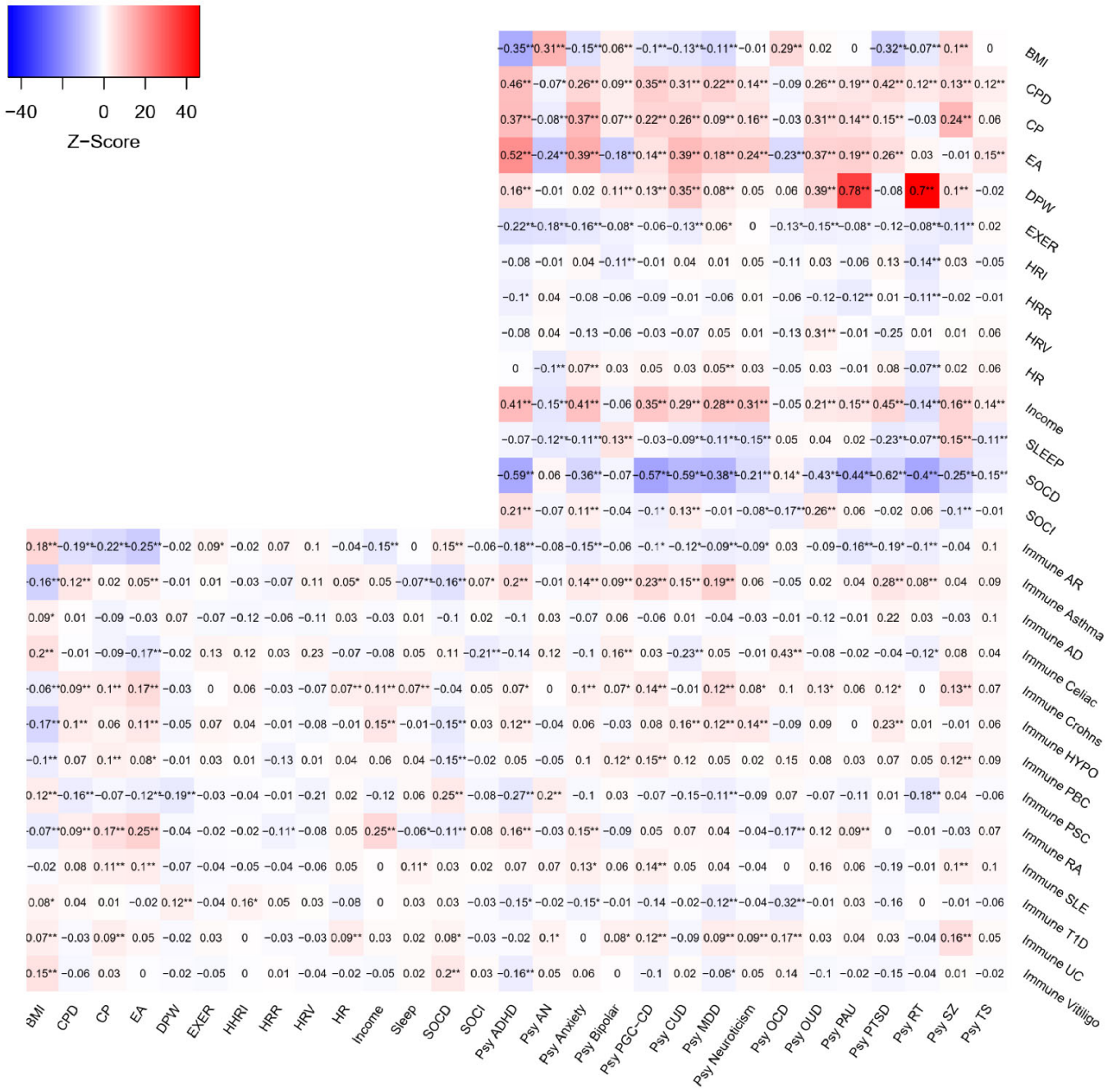
Supplementary Figures

eFigure 1. Flow Chart of the Study Design and Analysis Plan



S. Figure 1 Legend. Study design and analysis plan with miniaturized depictions of the corresponding Figures and S. Figures to orient and guide readers. The top-left panel depicts literature and databases searched for relevant GWAS summary statistics. The mid-left panel depicts LD-score regression (LDSC) analysis to estimate SNP heritability Z-score, resulting in a final set of phenotypes. The bottom-left panel depicts pairwise evaluation of genetic correlations among psychiatric, immune-related, and third variable phenotypes using LDSC. A set of 44 correlated psychiatric-immune pairs (FDR $q < 0.05$) were investigated for bidirectional Mendelian randomization (MR) effects with sensitivity analyses. Multivariable MR (MVMR) was used to adjust for effects of additional phenotypes (depicted in the bottom-center panel). Significant psychiatric instrument loci with positive effects on immune outcomes were interrogated for enriched genes, tissues, and gene-sets using FUMA's *GENE2FUNCTION* analysis (middle-center panel). For phenotype pairs demonstrating robust MR effects, two-sided GWAS meta-analysis identified subsets of SNPs with concordant and discordant effects (bottom right panel), and these SNP subsets were characterized for enriched genes tissues, cell-types, gene-sets, and genes was performed with FUMA SNP2GENE function (middle-center panel).

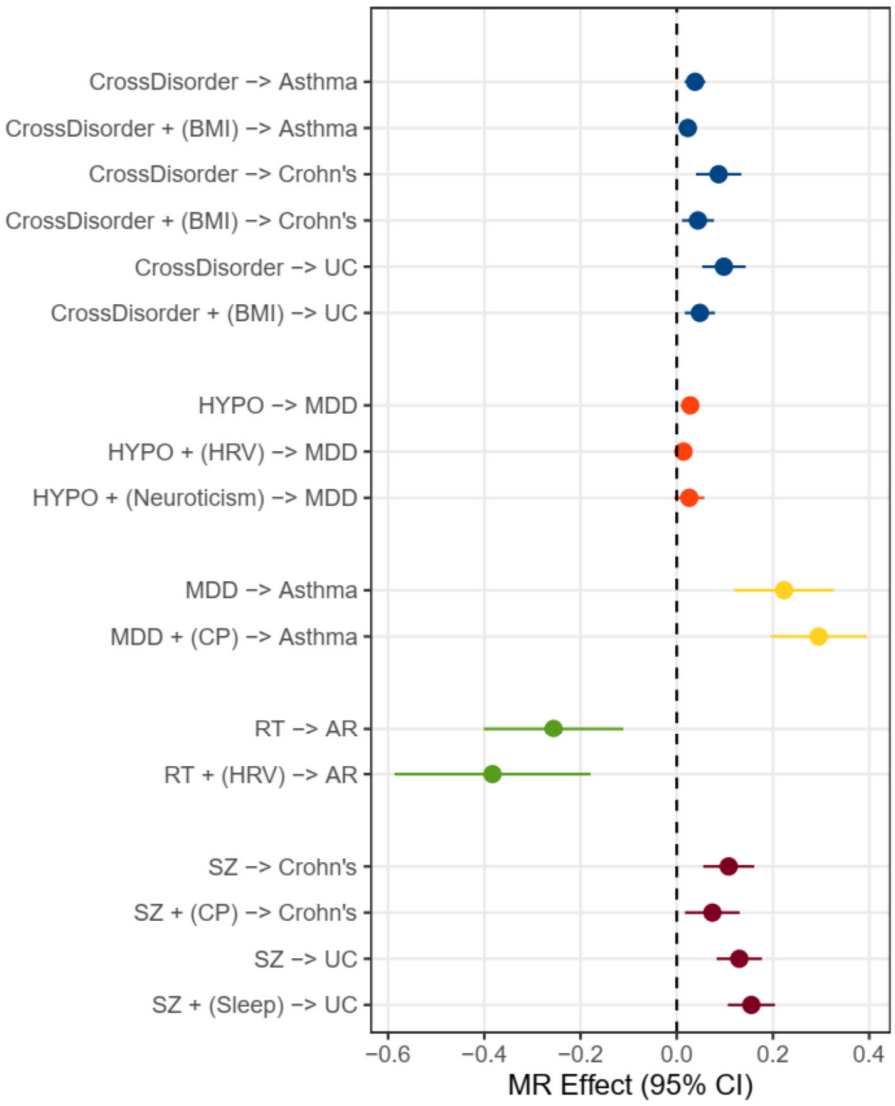
eFigure 2. Genetic Correlations Among Psychiatric Disorders and Immune-Related Traits and Other Risk Factors



Genetic correlation coefficients (text) and z-score (color) between psychiatric (X-axis), immune-related (Y-axis), and third variable phenotypes (both axes). Increasing intensity of red color indicates positive correlations and increasing intensity of blue indicates negative correlations. Correlations reaching uncorrected $p < 0.05$ are denoted with *, while those reaching false discovery rate $q < 0.05$ (reflecting correction for a total 587 unique tests) are denoted with **. Abbreviations include allergic rhinitis (AR), anorexia nervosa (AN), atopic dermatitis (AD), attention-deficit hyperactivity disorder (ADHD), body mass index (BMI), cannabis use disorder (CUD), cigarettes per day (CPD), cognitive processing (CP), alcoholic drinks per week (DPW), educational attainment (EA), frequency of moderate intensity exercise (EXER), heart rate (HR), heart rate increase during exercise (HRI), heart rate recovery after exercise (HRR), heart rate variability (HRV), hypothyroidism (HYPO), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), primary biliary cirrhosis (PBC),

primary sclerosing cholangitis (PSC), problematic alcohol use (PAU), rheumatoid arthritis (RA), risk-tolerance (RT), sleep duration (SLEEP), social deprivation *via* the Townsend Index (SOCD), social interaction frequency (SOCI), schizophrenia (SZ), systemic lupus erythematosus (SLE), Tourette's syndrome (TS), type 1 diabetes (T1D), ulcerative colitis (UC). Full results are also provided in S. Table 2.

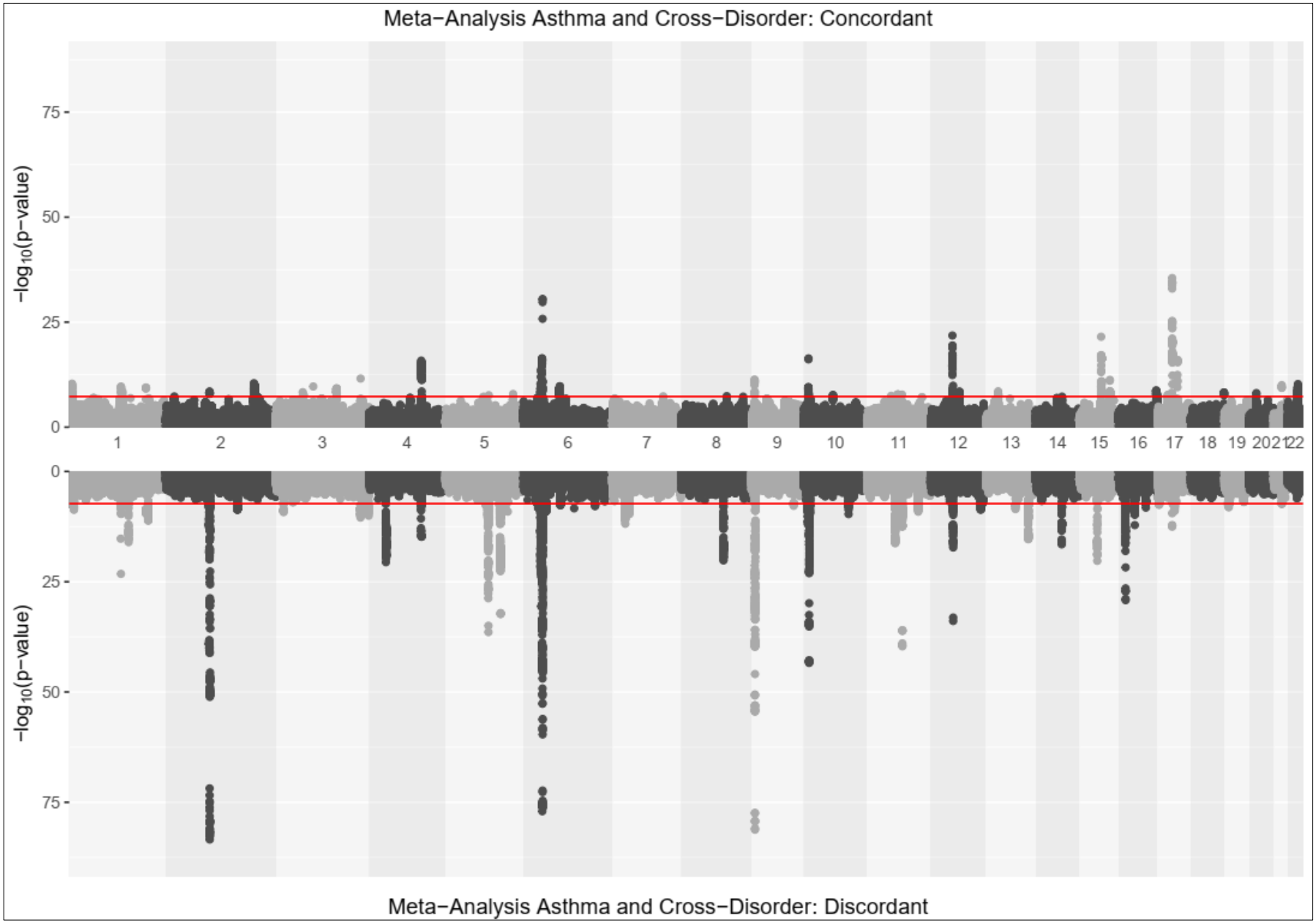
eFigure 3. MVMR Effects After Adjustment for Other Risk Factors



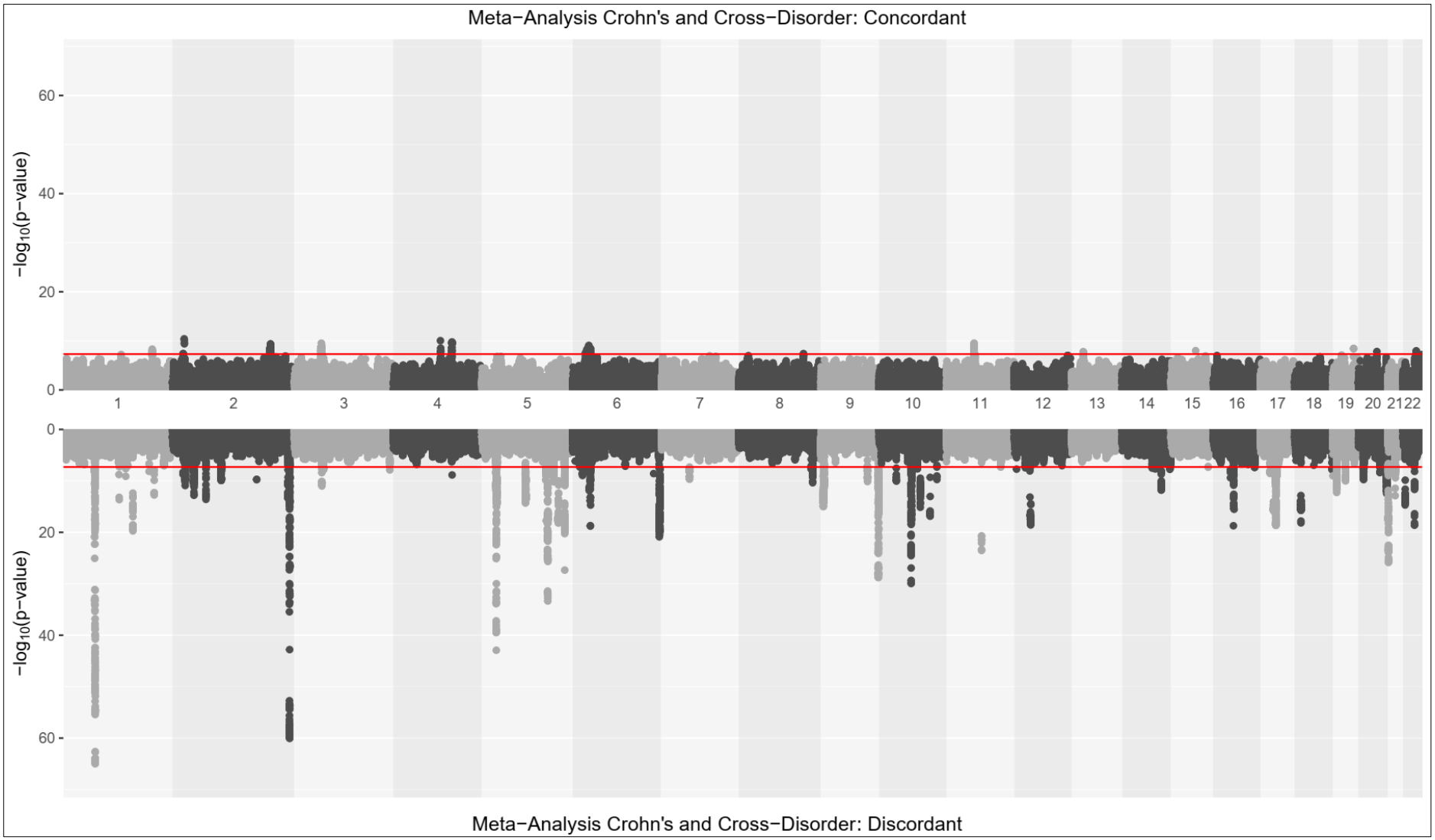
Multivariable Mendelian randomization results, depicting effect sizes with 95% confidence intervals with and without adjustment for the additional phenotypes. Full results of these analyses are provided in S. Table 3. Abbreviations include body mass index (BMI), cognitive processing (CP), heart rate variability (HRV), hypothyroidism (HYPO), major depressive disorder (MDD), schizophrenia (SZ), ulcerative colitis (UC).

eFigure 4. A through F. Miami Plots Depicting Concordant and Discordant Effects Identified via 2-Sided Meta-Analysis of Psychiatric-Immune Phenotype Pairs

4A.



4B.



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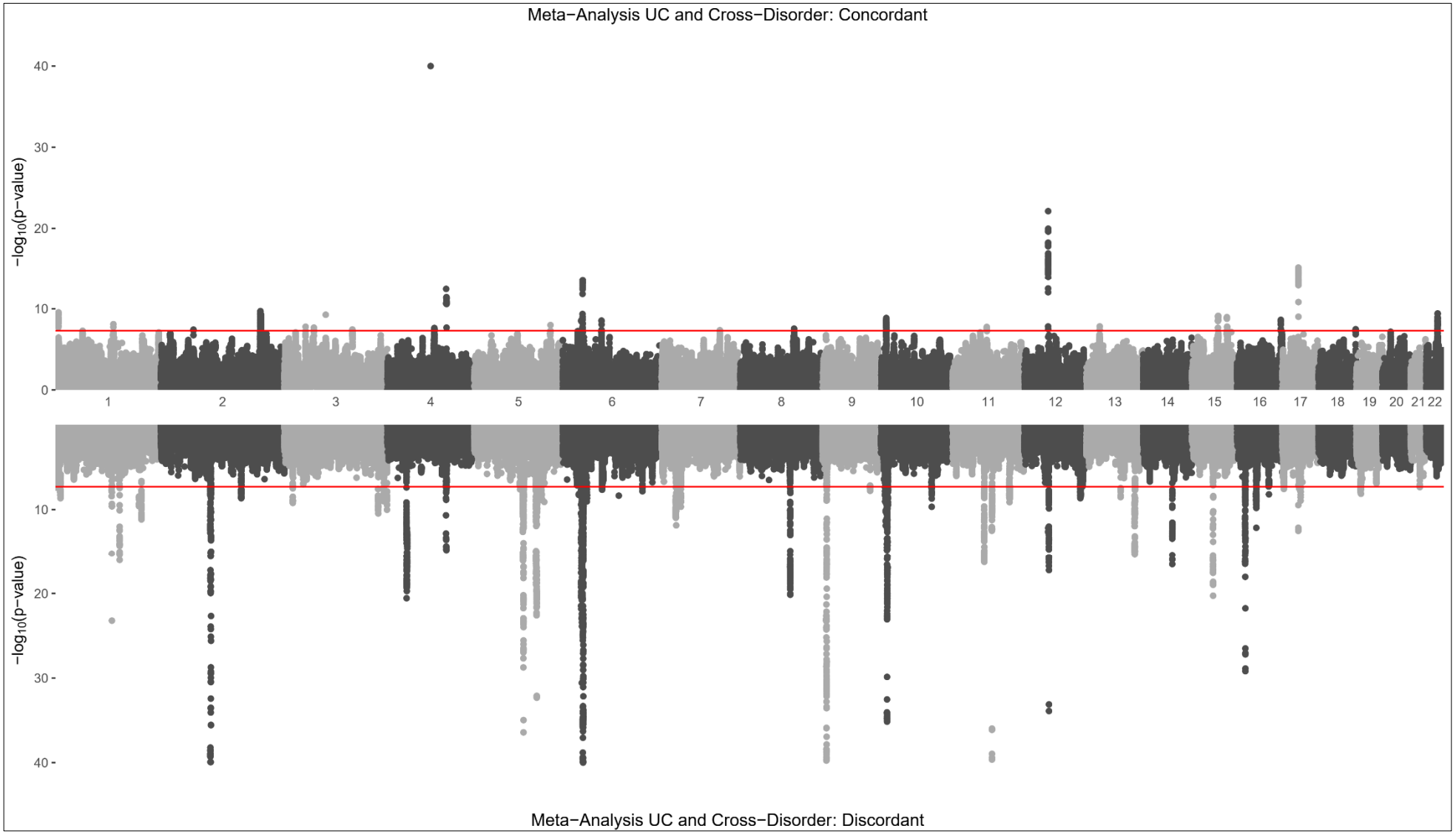
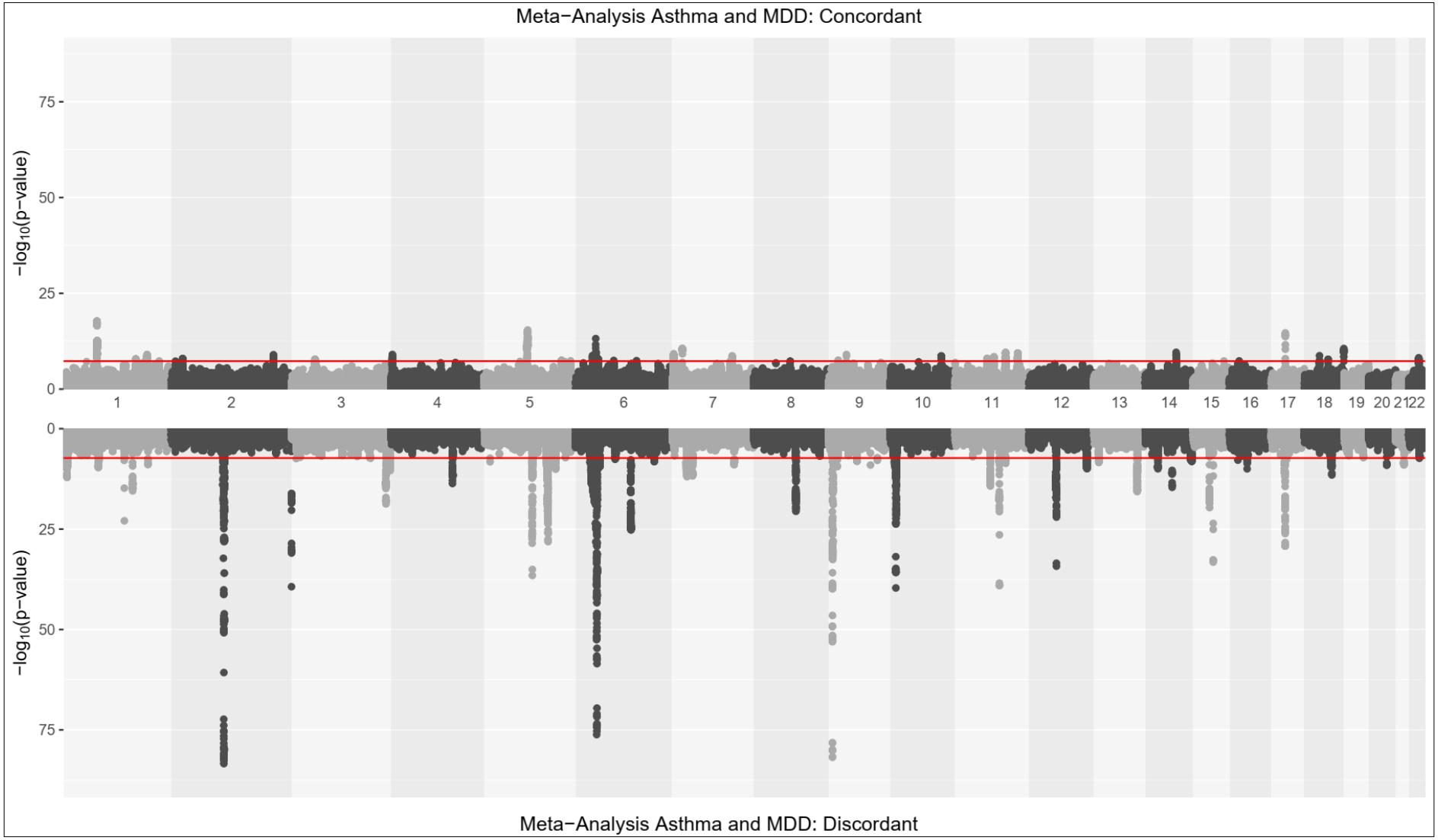
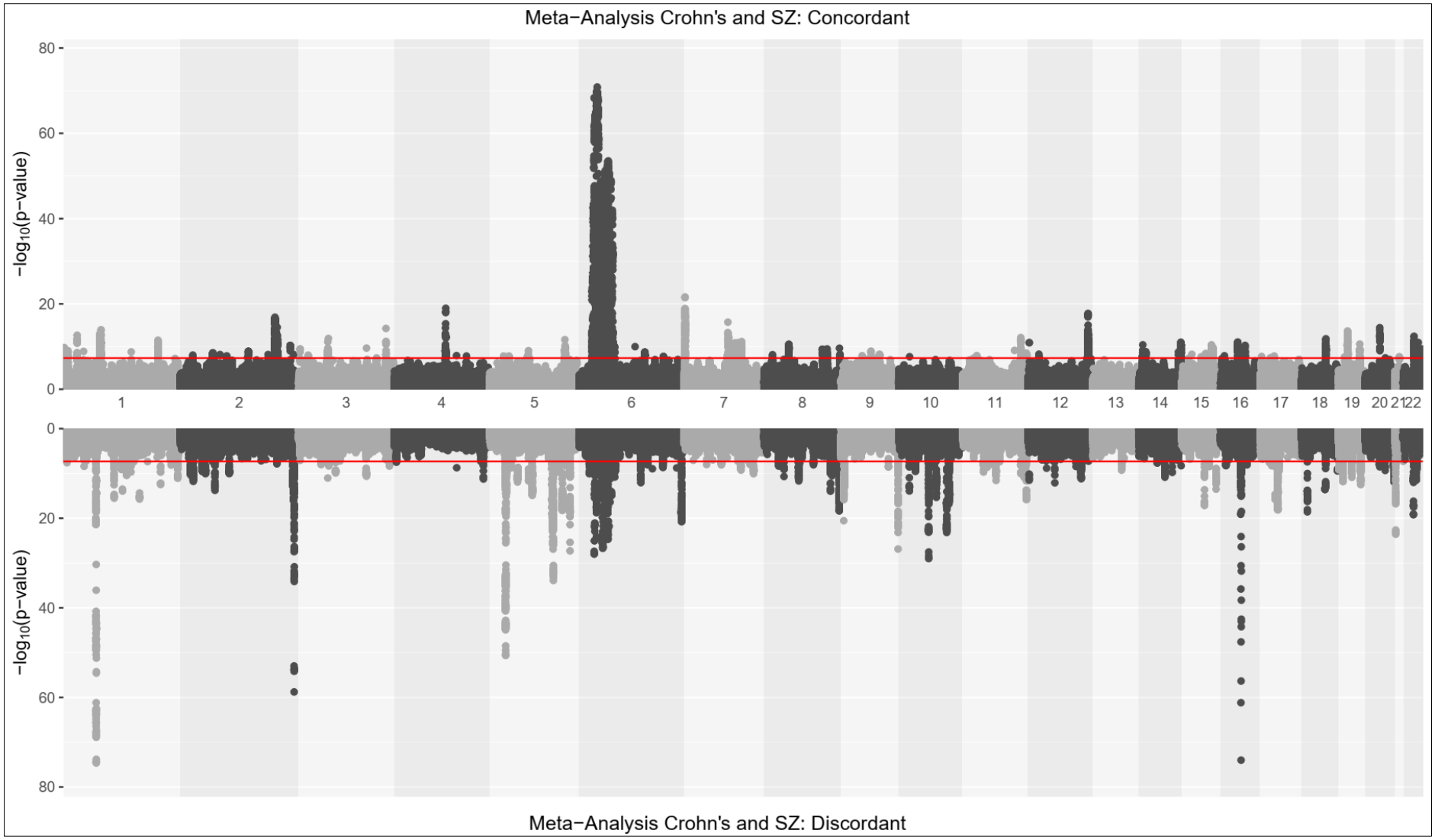


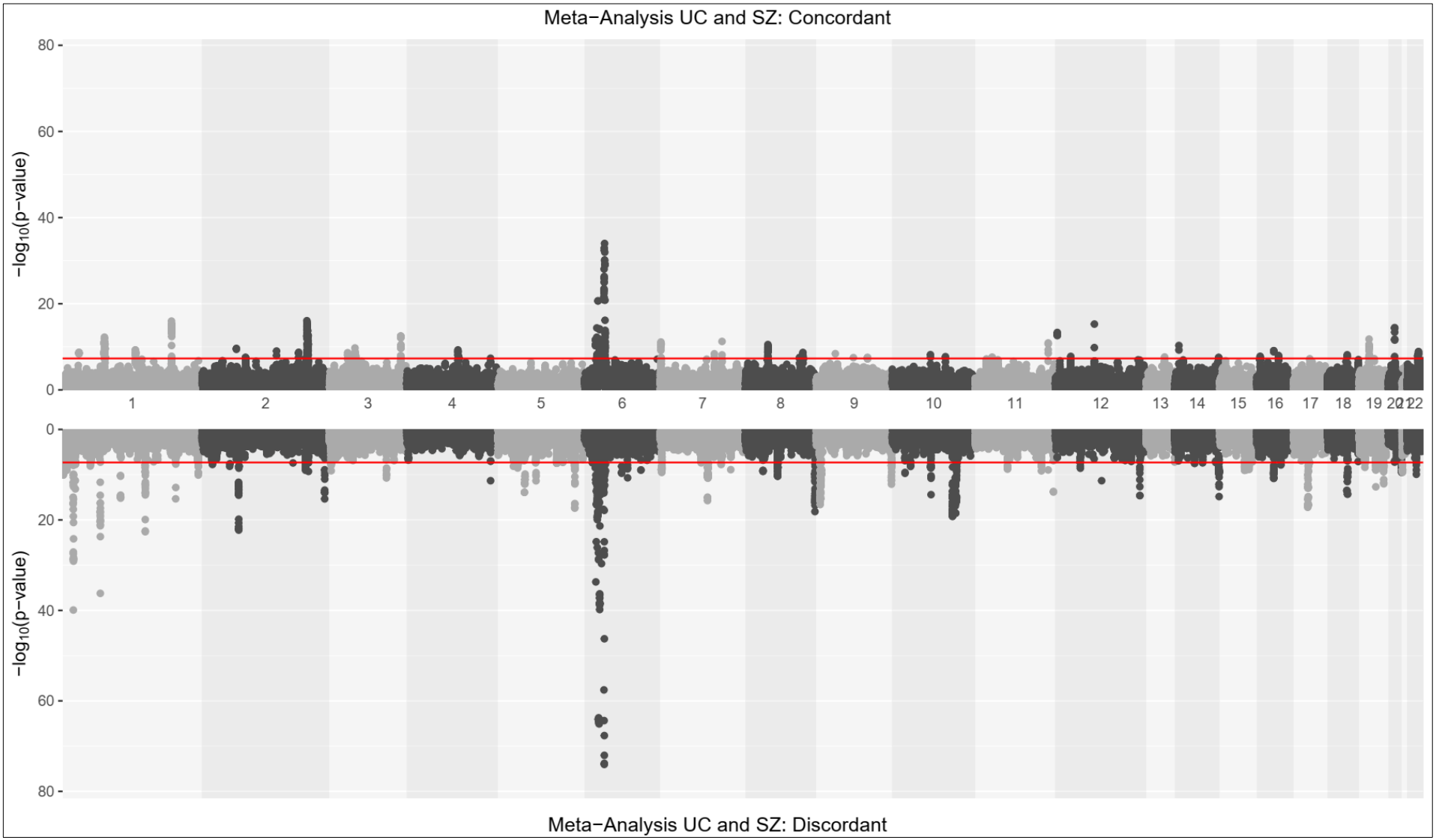
4D.



4E.



4F.



S. Figures 4 Legend. Miami plots depicting the results of ASSET two-sided meta-analysis of psychiatric-immune phenotype pairs (limited to case-control data only), such that the top of the plot reflects SNPs with significantly concordant effect for both phenotypes, and the bottom plot reflects SNPs with significantly discordant effect for both phenotypes. Y-axes reflect the magnitude of the $-\log_{10}(p\text{-value})$ and all plots have the same y-axis limits to facilitate comparison. The red line depicts the threshold for genome-wide significance ($5x10^{-8}$). Details for each of the LD-independent genome-wide loci are provided in S. Table 6.

eFigure 5. A & B. Tissue and Cell Type Enrichment Analyses of Loci With Concordant and Discordant Effects Within the Psychiatric-Immune Associations Identified

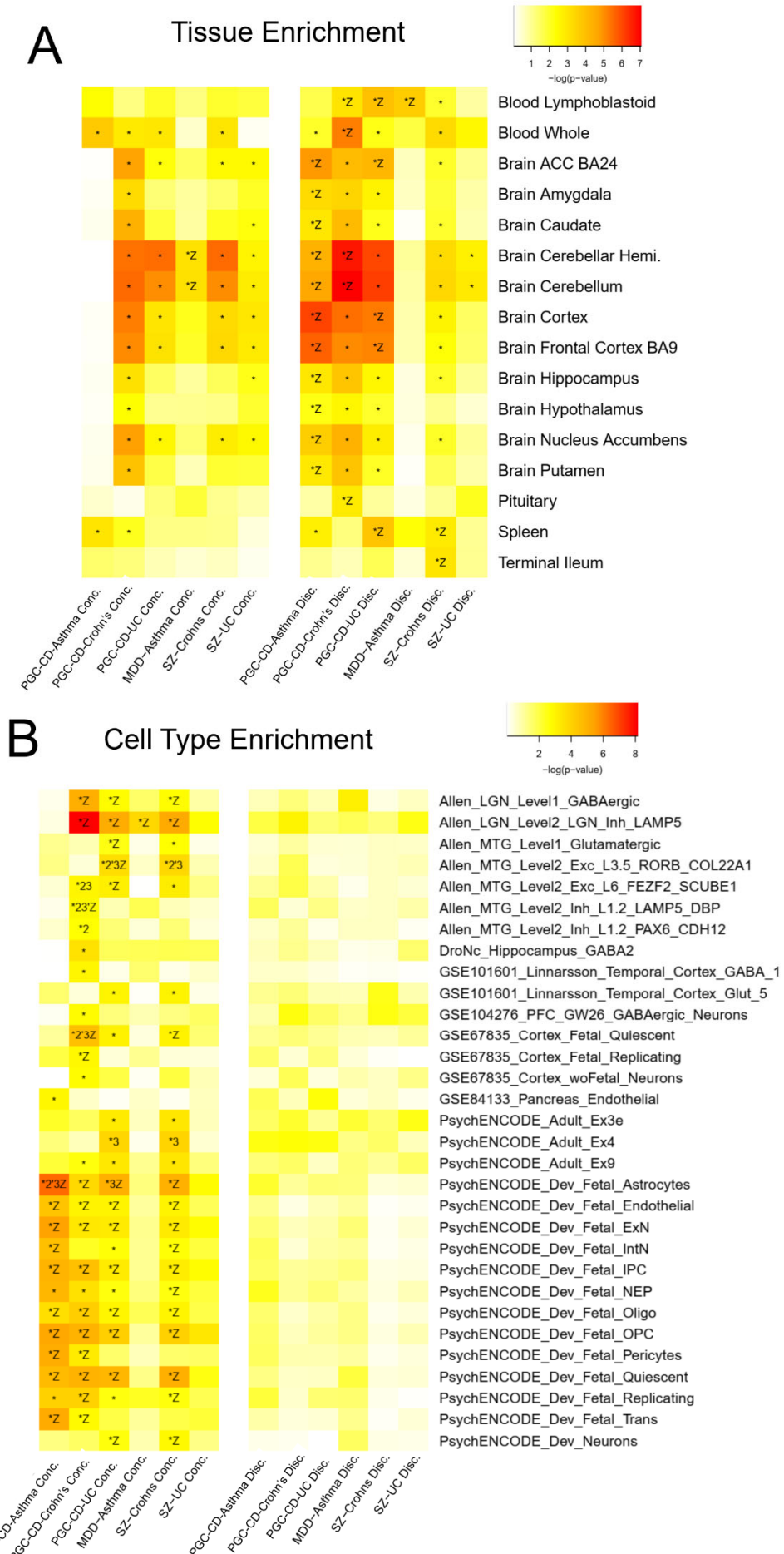


Figure 5 Legend. Tissue and cell type enrichment results performed on concordant (Conc.) and discordant (Disc.) SNP subsets generated with respect to psychiatric-immune phenotype pairs. Color intensity reflects $-\log_{10}(p)$ of the enrichment *p*-value. *P*-values were corrected by applying the false discover rate (FDR) multiple testing correction per database and significant findings (FDR $q < 0.05$) are denoted with *. Differences in enrichment effects between respective concordant and discordant effects based on two-tailed *Z*-test are indicated using "Z" to denote the more significant enrichment. We display all terms with significant enrichment among at least 1 concordant SNP subsets, will full results in S. Table 7. **Panel A** depicts tissue-level enrichment analyses conducted using eQTL data from the GTEXv8 database. **Panel B** depicts cell type enrichment analyses using all human datasets provided within the FUMA interface. Numerical symbols within the heatmap denote the results of conditioned significance analyses; cell types for which Step 2 (*i.e.*, within reference data set conditioning) average proportional significance [PS] $\geq$ 0.8 are denoted with 2, whereas 2' denotes the cell type with the highest average Step 2 PS when none reached the threshold of 0.8. Similarly, 3 and 3' indicate annotations with an average PS $\geq$ 0.8 and the highest average PS when none reached this threshold. Full names of gene-sets can be searched within the Molecular Signature Database for detailed descriptions. Abbreviations include: ACC (anterior cingulate cortex), Brodmann's area (BA), the PGC cross-disorder phenotype (PGC-CD), developmental (Dev.), excitatory (Ex), gestational week (GW), hemisphere (Hemi), inhibitory (Inh), lateral geniculate nucleus (LGN), major depressive disorder (MDD), middle temporal gyrus (MTG), neuroepithelial cells (NEP), oligodendrocyte precursor cells (OPC), prefrontal cortex (PFC), schizophrenia (SZ), and ulcerative colitis (UC).