Not just one *p*: Multivariate GWAS of psychiatric disorders and their cardinal symptoms reveal two dimensions of cross-cutting genetic liabilities

Travis T. Mallard[1], Richard K. Linnér[2, 3], Aysu Okbay[2], Andrew D. Grotzinger[1], Ronald de Vlaming[2,4], S. Fleur W. Meddens[2,4], Elliot M. Tucker-Drob[1,5], Kenneth S. Kendler[6,7], Matthew C. Keller[8,9], Philipp D. Koellinger[2,4]*, & K. Paige Harden[1,5*]

[1]Department of Psychology, University of Texas at Austin, Austin, TX, USA

[2]Department of Economics, School of Business and Economics, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

[3]Autism and Developmental Medicine Institute, Geisinger, Lewisburg, PA

[4]Department of Applied Economics, Erasmus School of Economics, Erasmus University Rotterdam, Rotterdam, the Netherlands

[5]Population Research Center, University of Texas at Austin, Austin, TX USA

[6]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

[7]Department of Psychiatry, Medical College of Virginia/Virginia Commonwealth University, Richmond, VA, USA

[8]Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, CO, USA

[9]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO, USA

*Work was jointly supervised by these authors.

Correspondence to:

Travis T. Mallard, M.A., Department of Psychology, The University of Texas at Austin, 108 E. Dean Keeton Street, Stop A8000, Austin, TX 78712, USA. E-mail: travis.mallard@utexas.edu

K. Paige Harden, Ph.D., Department of Psychology, The University of Texas at Austin, 108 E. Dean Keeton Street, Stop A8000, Austin, TX 78712, USA. E-mail: harden@utexas.edu

Abstract

A single dimension of general psychopathology, *p*, has been hypothesized to represent a general liability that spans multiple types of psychiatric disorders and non-clinical variation in psychiatric symptoms across the lifespan. We conducted genome-wide association analyses of lifetime symptoms of mania, psychosis, irritability in 124,952 to 208,315 individuals from UK Biobank, and then applied Genomic SEM to model the genetic relationships between these psychiatric symptoms and clinically-defined psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder). Two dimensions of cross-cutting genetic liability emerged: general vulnerability to self-reported symptoms (p_{self}) versus transdiagnostic vulnerability to clinically-diagnosed disease ($p_{clinician}$). These were only modestly correlated (r_g = .344). Multivariate GWAS identified 145 and 11 independent and genome-wide significant loci for $p_{clinician}$ and p_{self}, respectively, and improved polygenic prediction, relative to univariate GWAS, in hold-out samples. Despite the severe impairments in occupational and educational functioning seen in patients with schizophrenia and bipolar disorder, p_{self} showed stronger and more pervasive genetic correlations with facets of socioeconomic disadvantage (educational attainment, income, and neighborhood deprivation), whereas $p_{clinician}$ was more strongly associated with medical disorders unrelated to the brain. Genetic variance in $p_{clinician}$ that was unrelated to general vulnerability to psychiatric symptoms was associated with *less* socioeconomic disadvantage, suggesting positive selection biases in clinical samples used in psychiatric GWAS. These findings inform criticisms of psychiatric nosology by suggesting that cross-disorder genetic liabilities identified in GWASs of clinician-defined psychiatric disease are relatively distinct from genetic liabilities operating on self-reported symptom variation in the general population.

Introduction

Psychiatric nosology draws boundaries between normality and abnormality, and between different types of abnormality (1,2). However, genome-wide association studies (GWASs) have found that psychiatric disorders have a massively polygenic architecture, with near-ubiquitous genetic correlations among them (3–5). These genetic correlations have motivated arguments that current clinical boundaries are invalid, as they do not reflect the extensive overlap in underlying genetic liabilities (5). Following McKusick's classic paper on the nosology of genetic diseases (6), we term this the "lumping critique." Additionally, the polygenicity of psychiatric disorders has re-invigorated what we term the "dimensional critique": Clinically-defined disorders are alleged to represent the extreme (and arbitrarily-defined) ends of quantitative dimensions of risk encompassing the entire population (7–9).

Initiatives like the Research Domain Criteria (RDoC) (2), the Hierarchical Taxonomy of Psychopathology (HiTOP) (10), and proposed revisions to the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5*) (11) have advanced both the lumping and the dimensional critiques, arguing that the pathogenic processes underlying psychiatric disease cut across the boundaries between different diagnostic entities and across the boundaries between normality and abnormality (12). Perhaps the most radical expression of this view is the proposal that *all* forms of psychiatric disease share a common set of pathogenic processes, which can be investigated using a latent factor, *p*. The *p* factor has been conceptualized as representing a general liability to psychiatric symptoms that cuts across diagnostic entities, across the range of symptom severity, and across the lifespan (13,14). Although the lumping and the dimensional critiques are frequently advanced together to challenge psychiatric nosology, they are separable. Psychiatric diseases might share

underlying pathogenic processes without those same processes operating throughout the entire range of symptoms.

Moreover, debates about psychiatric nosology often implicitly assume that the same model will be true for all forms of psychopathology, when, in fact, some diagnostic entities might be better conceptualized as extreme ends of a continuous distribution than others (15–17). The lumping and dimensional critiques of psychiatric nosology have been most hotly debated with regard to schizophrenia and bipolar disorder (18–22). Some theorists propose that disorders such as schizophrenia and schizoaffective disorder should be replaced by a dimensional psychosis spectrum (18,19). Proponents of this model argue that psychotic experiences, including mania, are common in the general population and exhibit phenomenological and temporal continuity with psychotic disorders (23,24). However, others have reported that psychotic experiences in the general population share nonspecific, bi-directional associations with a wide range of mental disorders (25–28) and can reflect misinterpretations of normative experiences (26).

The validity of the dimensional critique has also fed into debates about GWAS research design. If valid, embracing "minimal phenotyping" in non-clinical samples has the potential to accelerate genetic discovery via dramatic increases in sample size, as self-report survey measures of psychiatric symptoms can be administered at scale to population-based or convenience samples. In contrast, clinical-level pathology is currently demarcated not only by severity of symptoms, but also by their co-occurrence within a specified timeframe. This requires a phenotypic approach that can be slow, difficult, and costly. The argument for minimal phenotyping has been forwarded in recent GWASs that have jointly analyzed clinically-defined depression phenotypes, depressive symptoms, and related traits such as neuroticism and subjective well-being (8,29). Others have

argued, however, that minimal phenotyping might preferentially detect genetic variants that are non-specific to any one disorder (30).

Previous efforts to use molecular genetic data to inform psychiatric nosology and GWAS research design have typically addressed either the dimensional or the lumping critique, but not both. Addressing the dimensional critique, previous studies have examined the genetic correlation between a single clinically-defined disorder and normal-range symptom variation, e.g., between attention-deficit hyperactivity disorder diagnoses and attention-deficit hyperactivity disorder symptom counts (15). These studies, however, have not typically incorporated genetic data from multiple clinically-defined diagnostic entities. Alternatively, addressing the lumping critique, previous studies have documented genetic relationships among clinical-defined disorders (5) but have not extensively probed the extent to which the genetic overlap among them can be projected downward into the normal range of symptom variation.

The present paper addresses both the lumping and dimensional critiques by conducting a multivariate GWAS of multiple clinically-defined disorders and of normal-range variation in these disorders' cardinal symptoms. First, we conducted GWASs of lifetime symptoms of irritability, mania, and psychosis in a population-based sample, and examine the pairwise genetic correlations among these symptom dimensions, depressive symptoms, and lifetime diagnoses of serious psychiatric disorders (schizophrenia, bipolar disorder, and major depressive disorder). Next, we apply Genomic SEM (31) to test formal models of the genetic covariance among multiple psychiatric disorders and symptom dimensions.

Method

Genome-wide association analyses

Using unrelated, European-ancestry participants in UK Biobank, we conducted GWASs of irritability (1 symptom; $N = 205{,}270$), mania (up to 9 symptoms; $N = 208{,}315$), and psychosis (up to 6 symptoms; $N = 124{,}952$). Sample description, study procedure, and quality control protocol are described in Supplementary Note section 1. Symptoms were assessed on up to two occasions, and item-level reports across measurement occasions were combined using a Bayesian item-response theory model (32,33) (Supplementary Note sections 2-4). Association analyses were performed using a SNPtest (34) and EasyQC (35) pipeline.

Gene-based association and gene set enrichment analyses

We used MAGMA version 1.07 (Multi-marker Analysis of GenoMic Annotation) (36) to conduct gene-based association and gene-set enrichment analyses (Supplementary Note section 5). For the gene-based association analyses, we used default MAGMA parameters and standard procedures for gene-based association analyses based on summary statistics. For gene set enrichment analyses, we tested 5,917 gene sets corresponding to 4436 biological processes, 580 cellular components, and 901 molecular functions.

Heritability and genetic correlation analyses

We used Linkage Disequilibrium (LD) Score regression to estimate heritabilities, partitioned heritabilities, and genetic correlations among seven core phenotypes: symptoms of irritability, mania, and psychosis, which were the focus of our novel GWASs; symptoms of depression, which were analyzed in a previous large-scale GWAS (29); and three psychiatric disorders (bipolar disorder, schizophrenia, major depressive disorder) (8,37,38) that are characterized by these symptoms (Supplementary Note section 6). These GWASs and their phenotypes are described in Table 1. We also used LD Score regression to estimate genetic correlations among the latent factors estimated in our Genomic SEM analyses and related traits.

Genomic structural equation modeling

Genomic SEM, a statistical method that provides a flexible framework for applying structural equation modeling methods to GWAS results, was used to test a series of four confirmatory factor models, which were informed by psychiatric and psychometric theory (31) (Supplementary Note section 8). After we identified the best-fitting confirmatory factor model, we conducted a multivariate GWAS that estimated individual SNP effects on each latent factor (Supplementary Note section 8). Finally, we used a multivariate regression framework to estimate a series of partial genetic correlations between latent factors of psychopathology and related sociodemographic and medical traits. All reported estimates in the main text were derived from weighted least squares estimation, but estimates derived from maximum likelihood estimation are reported in the supplementary materials.

Polygenic prediction analyses

UK Biobank. We conducted a series of polygenic score analyses predicting (i) symptoms of irritability, mania, and psychosis, as well as (ii) bipolar disorder, schizophrenia, and schizoaffective disorder case status in UK Biobank holdout samples (Supplementary Note section 1). Polygenic scores were constructed for seven univariate GWAS phenotypes and two multivariate GWAS phenotypes. For all polygenic scores, we restricted variants to bi-allelic HapMap3 SNPs that were present in both the summary statistics and the prediction sample. We then used LDpred (39) to correct for the LD between SNPs and PLINK 1.9 (40) to calculate a polygenic score for each participant (Supplementary Note sections 7 & 11).

Philadelphia Neurodevelopmental Cohort. We further tested the validity of our multivariate GWAS results in the Philadelphia Neurodevelopmental Cohort, an independent sample of youths aged 8 to 21 (Supplementary Note section 11). Specifically, we tested a series of

models with polygenic scores for *p* factors predicting latent factors of general psychopathology, thought problems, internalizing problems, and externalizing problems. Polygenic scores were constructed as in UK Biobank.

Results

Univariate GWAS of irritability, mania, and psychosis detects 11 loci associated with psychiatric symptoms

The quantile–quantile plots (Supplementary Figure 3) exhibit inflation of the median test statistic for irritability (λ_{GC} = 1.197), mania (λ_{GC} = 1.178), and psychosis (λ_{GC} = 1.038). The estimated intercept from LD Score regression suggests that nearly all the inflation for irritability (0.9965), mania (1.013), and psychosis (1.002) is due to polygenic signal rather than bias. Using a clumping procedure (Supplementary Note), we identified 6, 4, and 1 approximately independent SNPs reaching genome-wide significance (*i.e.*, lead SNPs) for irritability, mania, and psychosis, respectively, with 1 lead SNP overlapping across irritability and mania (Supplementary Figure 3; Supplementary Table 5). Systematic queries of the NHGRI-EBI GWAS Catalog revealed that one lead SNP (rs9862795) is in moderate-to-high LD with SNPs previously associated with educational attainment (41), intelligence (41), and depressed affect (42). Other SNPs yielded no matches in the NHGRI-EBI GWAS Catalog and can be considered novel loci.

Gene-wise analyses identified, after correcting for multiple testing, 25 significant genes associated with mania and 25 associated with irritability (9 of which overlap across phenotypes; Supplementary Table 7). In Supplementary Note section 5, we discuss some of these genes in more detail, including: *DRD2*, *CAMKV*, and *IP6K1*. No gene emerged as significantly associated with psychosis. No gene sets were associated with the irritability, mania, or psychosis phenotypes after correction for multiple comparisons (Supplementary Table 8).

Partitioned heritability analyses indicate that several genomic annotations were enriched for irritability and mania, including: regions conserved in mammals, DNase hypersensitivity sites, fetal DNase hypersensitivity sites, and H3K9ac peaks (Supplementary Table 10). No genomic annotation was enriched for psychosis after correcting for multiple testing. There was little evidence of tissue-specific enrichment for irritability, mania, and psychosis after correcting for multiple testing (Supplementary Table 11), though several brain regions were enriched for irritability (Supplementary Note section 6).

Genetic correlations among symptom dimensions and psychiatric disorders identify two distinct dimensions of cross-cutting genetic liability

As illustrated in **Figure 1** (Supplementary Table 12), we observed large genetic correlations among pairs of psychiatric symptoms: irritability and mania (r_g = .880, *SE* = .020), mania and psychosis (r_g = .725, *SE* = .092), and mania and depression (r_g = .775, *SE* = .039). However, we observed smaller genetic correlations between some psychiatric disorders and their cardinal symptoms, such as between bipolar disorder and mania (r_g = .245, *SE* = .040), bipolar disorder and irritability (r_g = .156, *SE* = .038), and schizophrenia and psychosis (r_g = .405, *SE* = .067).

We next formally modeled the genetic covariance matrix using Genomic SEM (Supplementary Figure 6), testing four confirmatory factor models: (i) Model A, a common factor model with all indicators loading onto a single latent *p* factor, as has been previously proposed (13,14); (ii) Model B, a correlated factors model with indicators loading onto latent factors of affective versus psychotic psychopathology, (iii) Model C, a correlated factors model with indicators loading onto distinct latent *p* factors for psychiatric disorders and symptom dimensions, and (iv) Model D, a correlated factors model with indicators loading onto distinct latent *p* factors

for clinician- and self-rated psychopathology, allowing for cross-loadings when studies combined measurement approaches. Model comparisons are summarized below and further described in the supplementary materials (Supplementary Note section 8, Supplementary Table 20 & 21). Only Model D showed good fit to the data (χ^2 (11) = 196.82, AIC = 230.82, CFI = .952, SRMR = .059) (**Figure 2**). There was not just one *p*: The patterns of genetic covariance between symptom dimensions and psychiatric disorders were most parsimoniously represented by $p_{clinician}$ and p_{self}, which were correlated only modestly (r_g = .344).

Multivariate GWAS of *p* factors

In multivariate GWAS testing associations between individual SNPs and latent factors, we observed inflation of the median test statistic for both $p_{clinician}$ (λ_{GC} = 1.585) and p_{self} (λ_{GC} = 1.403). The estimated intercept from LD Score regression for $p_{clinician}$ and p_{self} (0.9751 and 0.9911, respectively) suggests that nearly all the inflation is due to polygenic signal rather than bias (**Figure 3**). Using the clumping procedure described in the Supplementary Note, we identified 145 and 11 approximately-independent lead SNPs for $p_{clinician}$ and p_{self}, respectively (Supplementary Table 22).

After correcting for multiple testing, gene-wise analyses identified 370 genes associated with $p_{clinician}$ and 47 genes associated with p_{self} (Supplementary Table 24). Sixty-two of the genes associated with $p_{clinician}$ and twenty-one of the genes associated with p_{self} can be considered novel, as they were not associated with any of the constituent GWAS phenotypes. Moreover, only 11 genes were associated with both *p* factors. We discuss some of the genes associated with the *p* factors in Supplementary Note section 9, such as *RBFOX1*. The results of gene set enrichment analyses are further consistent with a distinction between $p_{clinician}$ and p_{self}, as no gene sets were associated with both *p* factors (Supplementary Note section 9, Supplementary Table 26). Results

for $p_{clinician}$ and p_{self} begin to converge on similar biological systems only at a less-granular level of analysis. Partitioned heritability results indicate that similar functional annotations across the genome were enriched for both $p_{clinician}$ and p_{self}, as were various brain tissues (Supplementary Note section 10; Supplementary Tables 27-28).

Polygenic score analyses in hold-out samples (i) supported the validity of the multivariate GWAS results, and (ii) demonstrated that multivariate GWAS generally improved polygenic prediction relative to univariate GWAS (Supplementary Figures 7-8; Supplementary Tables 13-19, 30-31). Compared to the best univariate PGS, $p_{clinician}$ resulted in a ~1.10-fold average increase in ΔR^2 and p_{self} resulted in a ~1.65-fold average increase. Overall, the $p_{clinician}$ polygenic score demonstrated greater predictive ability for clinician-rated diagnoses (R^2 ranging from 2.48% to 6.30%) than p_{self} (R^2 ranging from .45% to .73%), whereas the p_{self} polygenic score demonstrated greater predictive ability for self-rated symptoms (R^2 ranging from .14% to 1.10%) than $p_{clinician}$ (R^2 ranging from .02% to .31%) (**Figure 4**). We observed a similar pattern of results in the Philadelphia Neurodevelopmental Cohort (N = 4,551), where the p_{self} polygenic score was positively associated with a general factor of psychopathology constructed from self-report measures (pseudo R^2 = 1.34%, P = 2.69E-13), while $p_{clinician}$ was not (Supplementary Table 32).

Exploring the divergent genetic architecture between *p* factors

We identified pervasive correlations between p_{self} and worse cognitive performance, social disadvantage, and accelerated reproductive development and mortality (**Figure 4**; Supplementary Table 29). Notably, $p_{clinician}$ shows a more consistent pattern of genetic correlations with medical diagnoses unrelated to the brain, whereas p_{self} appears to capture the genetic liability toward worse social position more strongly than $p_{clinician}$. To further probe the latter finding, we used Genomic SEM to estimate the genetic correlations between the *p* factors and a latent genetic factor of general

social advantage, which captured genetic variance generally associated with social stratification in educational attainment, income, and (reverse-coded) area-based social deprivation (41,43). We then used a multivariate regression model that simultaneously regressed $p_{clinician}$ on social advantage and on p_{self} (Supplementary Figure 13). This analysis estimated the genetic correlation between social advantage and variance in $p_{clinician}$ that was distinct from $p_{self.}$ Additionally, this analysis estimated the genetic correlation between $p_{clinician}$ and p_{self} after statistically accounting for their diverging genetic correlations with social advantage. Full results are reported in Supplementary Tables 33-34.

There were three findings. First, consistent with bivariate genetic correlations reported above, p_{self} was negatively associated with social advantage (r_g = -.431, *SE* = .025). In contrast, the variance in $p_{clinician}$ unique of p_{self} had a positive genetic relationship with social advantage (b_g = .238, *SE* = .037). After accounting for their diverging relationships with social advantage, the genetic relationship between $p_{clinician}$ and p_{self} increased (b_g = .487, *SE* = .055; compared to r_g = .352, *SE* = .034 without controlling for social advantage).

Discussion

Widespread comorbidity (44) and ubiquitous genetic correlations (5) among disorders has motivated the proposal that a single dimension of liability, *p*, cuts across the boundaries between different diagnostic entities and across the boundary between normality and abnormality (13,14). Jointly analyzing GWAS data from seven psychiatric disorders and symptoms, we identified novel loci for psychiatric phenotypes. And, we found evidence for more than one *p*: The dimension of genetic risk that cuts across clinician-defined diseases was largely distinct from the dimension of genetic risk that cuts across self-reported symptoms. To make sense of this, consider five ways

clinician-rated psychopathology differs from self-reported symptoms: (i) severity, (ii) temporal clustering, (iii) heterogeneity of symptom type, (iv) insight, and (v) sources of selection.

First, people with clinically-defined psychiatric disorders have more numerous and severe symptoms than people who do not meet diagnostic-criteria. Dimensional models of psychopathology predict that the same dimension of genetic risk would underlie the entire range of symptom severity. However, polygenic scores calculated from case/control studies of schizophrenia are weak and inconsistent predictors of the severity of schizophrenia symptoms (45,46). Similarly, our results suggest that the severity of symptoms evident in clinical disorders might reflect a difference in kind, rather than merely in degree.

These results also suggest new possibilities for dimensional measurement. Currently, the most common approach to measuring psychopathology in non-clinical samples is to begin with the symptoms of *DSM*-5 or *ICD-10* disorders and ask people if they experience some symptoms, some of the time. An alternative approach is to begin with the genetic variants that are associated with clinical disorders and identify which phenotypes are characteristic of people in the general population who have elevated polygenic risk. For instance, polygenic risk for schizophrenia has been associated with illicit drug use in emerging adulthood and with anxiety rather than psychosis in adolescence (45,47). “Phenome-wide” association studies of polygenic scores derived from GWASs of psychiatric disorders might advance the construction of new dimensional measures of psychopathology (48–50).

Second, psychiatric disorders are defined by combinations of symptoms that might be heterogeneous with respect to genetic architecture, potentially attenuating the genetic correlation with any one symptom. For instance, low genetic correlation between clinician-rated schizophrenia

and self-rated psychotic symptoms might be due to genetic influences on symptom domains not assessed, such as negative symptoms.

Third, clinical assessment pays close attention to temporal frame during which symptoms co-occur (Supplementary Figure 14). In contrast, temporal clustering is not always considered in self-reports of symptoms. In UK Biobank, for example, the assessment of mania refers to symptoms that occur within a single period, but the measures of psychotic symptoms all refer to lifetime occurrence. Little work has considered whether the genetic etiology of a symptoms that occurs synchronously with another differs from the genetic etiology of that same symptom in temporal isolation.

Fourth, people have unique insight into their own internal mental states, but they lack perfect insight into how their behaviors are perceived by others, and they might be motivated to diminish their symptoms because of social desirability biases. The relatively modest genetic correlations between the *p* factors could reflect these asymmetries and biases. Moreover, some symptoms (*e.g.*, delusional thinking) themselves impair people's ability to report accurately on their psychological experiences.

Finally, samples of people with clinician-rated disorders (particularly when those disorders are rare and seriously impairing) are subject to different sources of selection, attrition, and non-response than population-based studies that utilize self-report surveys. Previous research has found that genetic variants associated with educational attainment and schizophrenia predict research participation (51,52). These selection processes could induce a collider bias, leading to misleading estimates of genetic correlations (53).

We conducted an initial exploration of the potential role of selection bias by estimating the unique genetic correlations between social advantage and both *p* factors. Although patients with

serious mental illness face severe educational and occupational impairments, we find that the genetic variance unique to clinician-rated disorders was associated with *less* socioeconomic disadvantage. This result suggests that patients represented in genetic association studies of schizophrenia, bipolar disorder, and major depressive disorder might be positively selected for social status. Consider, for instance, that incarcerated persons in Western countries are two- to four-times more likely than the general population to have a psychotic disorder (54), and the rate of serious mental illness in homeless populations is about 20% (55), but these socially-marginalized groups are less likely to have access to adequate mental health care or be included in medical research. At the same time, our GWASs of psychiatric symptoms rely on UK Biobank, a volunteer sample that is generally healthier and more socially advantaged than the UK population (56,57). As GWAS samples continue to grow, we expect that researchers will pay increasing attention to issues around population representativeness.

In conclusion, current psychiatric nosology has been criticized for failing to account for the ubiquitous genetic correlations among clinically-defined disorders and for embracing categorical disease entities rather than continuous dimensions of risk. We conducted the first-ever multivariate GWAS of multiple symptoms and disorders, and found that the genetic liabilities operating on self-reported symptom variation were largely distinct from the genetic liabilities operating on clinically-defined psychiatric diseases. These results refine criticisms of psychiatric nosology and suggest that further research is needed to understand cross-cutting genetic risks.

References

1. Kendler KS. An historical framework for psychiatric nosology. Psychol Med. 2009;39(12):1935–41.

2. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am Psychiatric Assoc; 2010.

3. Wray NR, Wijmenga C, Sullivan PF, Yang J, Visscher PM. Common Disease Is More Complex Than Implied by the Core Gene Omnigenic Model. Cell. 2018;173(7):1573–80.

4. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015;47(11):1236–41.

5. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, et al. Analysis of shared heritability in common disorders of the brain. Science (80-). 2018;360(6395):eaap8757.

6. McKusick VA. On Lumpers and Splitters, or the Nosology of Genetic Disease. Perspect Biol Med. 1969;12(2):298–312.

7. Smoller JW, Andreassen OA, Edenberg HJ, Faraone S V, Glatt SJ, Kendler KS. Psychiatric genetics and the structure of psychopathology. Mol Psychiatry. 2018;1.

8. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018 May;50(5):668–81.

9. Plomin R, Haworth CMA, Davis OSP. Common disorders are quantitative traits. Nat Rev Genet. 2009;10(12):872.

10. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol. 2017;126(4):454.

11. Association AP, others. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

12. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, et al. Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry. 2017 Oct;175(1):15–27.

13. Caspi A, Moffitt TE. All for One and One for All: Mental Disorders in One Dimension. Am J Psychiatry. 2018 Sep;175(9):831–44.

14. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. The p factor: One general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci. 2014;2(2):119–37.

15. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63–75.

16. Walters RK, Adams MJ, Adkins AE, Aliev F, Bacanu S-A, Batzler A, et al. Trans-ancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. bioRxiv. 2018 Mar;257311.

17. Robinson EB, St Pourcain B, Anttila V, Kosmicki JA, Bulik-Sullivan B, Grove J, et al. Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. Nat Genet. 2016 May;48(5):552–5.

18. Guloksuz S, Van Os J. The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. Psychol Med. 2018;48(2):229–44.

19. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016;15(2):118–24.

20. Parnas J, Henriksen MG. Epistemological error and the illusion of phenomenological continuity. World Psychiatry. 2016;15(2):126–7.

21. Tandon R. Conceptualizing psychotic disorders: don't throw the baby out with the bathwater. World Psychiatry. 2016;15(2):133–4.

22. Ruderfer DM, Ripke S, McQuillin A, Boocock J, Stahl EA, Pavlides JMW, et al. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell. 2018;173(7):1705–15.

23. Dominguez MDG, Wichers M, Lieb R, Wittchen H-U, van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr Bull. 2009;37(1):84–93.

24. Linscott RJ, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med. 2013;43(6):1133–49.

25. Kendler KS, McGuire M, Gruenberg AM, Walsh D. Schizotypal symptoms and signs in the Roscommon Family Study: Their factor structure and familial relationship with psychotic and affective disorders. Arch Gen Psychiatry. 1995;52(4):296–303.

26. Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample: the National Comorbidity Survey. Arch Gen Psychiatry. 1996;53(11):1022–31.

27. McGrath JJ, Saha S, Al-Hamzawi A, Andrade L, Benjet C, Bromet EJ, et al. The bidirectional associations between psychotic experiences and DSM-IV mental disorders.

Am J Psychiatry. 2016;173(10):997–1006.

28. Saha S, Scott JG, Varghese D, McGrath JJ. The association between general psychological distress and delusional-like experiences: a large population-based study. Schizophr Res. 2011;127(1–3):246–51.

29. Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet. 2016;48(6):624–633.

30. Cai N, Kendler K, Flint J. Minimal phenotyping yields GWAS hits of low specificity for major depression. bioRxiv. 2018 Oct;440735.

31. Grotzinger AD, Rhemtulla M, Vlaming R de, Ritchie SJ, Mallard TT, Hill WD, et al. Genomic SEM Provides Insights into the Multivariate Genetic Architecture of Complex Traits. bioRxiv. 2018;305029.

32. Curran PJ, Hussong AM, Cai L, Huang W, Chassin L, Sher KJ, et al. Pooling data from multiple longitudinal studies: the role of item response theory in integrative data analysis. Dev Psychol. 2008 Mar;44(2):365–80.

33. Sheng Y, Wikle CK. Bayesian multidimensional IRT models with a hierarchical structure. Educ Psychol Meas. 2008;68(3):413–30.

34. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet. 2007 Jul;39(7):906–13.

35. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Mägi R, et al. Quality control and conduct of genome-wide association meta-analyses. Nat Protoc. 2014;9(5):1192–212.

36. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: Generalized Gene-Set Analysis of GWAS Data. PLoS Comput Biol. 2015;

37. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. 2018;50(3):381–9.

38. Stahl E, Breen G, Forstner A, McQuillin A, Ripke S, Cichon S, et al. Genomewide association study identifies 30 loci associated with bipolar disorder. biorxiv. 2018;173062.

39. Vilhjálmsson BJ, Jian Yang HKF, Alexander Gusev SL, Stephan Ripke GG, Po-Ru Loh, Gaurav Bhatia R Do, Tristan Hayeck H-HW, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet. 2015;97(4):576–92.

40. Chang CC, Chow CC, Tellier LCAM, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: Rising to the challenge of larger and richer datasets. Gigascience. 2015;4(1).

41. Lee JL, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, et al. Gene discovery and polygenic prediction from a 1.1-million-person GWAS of educational attainment. Nat Genet. 2018;50:1112–21.

42. Nagel M, Watanabe K, Stringer S, Posthuma D, Sluis S. Item-level analyses reveal genetic heterogeneity in neuroticism. Nat Commun. 2018;9(1):905.

43. Hill WD, Hagenaars SP, Marioni RE, Harris SE. Molecular genetic contributions to social deprivation and household income in UK Biobank (n=112,151). bioRxiv. 2016;

44. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry. 2005 Jun;62(6):617–27.

45. Jones HJ, Stergiakouli E, Tansey K, Hubbard LM, Heron J, Cannon M, et al. Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. JAMA psychiatry. 2016;73(3):221–8.

46. Stepniak B, Papiol S, Hammer C, Ramin A, Everts S, Hennig L, et al. Accumulated environmental risk determining age at schizophrenia onset: a deep phenotyping-based study. The Lancet Psychiatry. 2014 Nov;1(6):444–53.

47. Mallard TT, Harden KP, Fromme K. Genetic risk for schizophrenia is associated with substance use in emerging adulthood: an event-level polygenic prediction model. Psychol Med. :1–9.

48. Bush WS, Oetjens MT, Crawford DC. Unravelling the human genome–phenome relationship using phenome-wide association studies. Nat Rev Genet. 2016 Mar;17(3):129–45.

49. Krapohl E, Euesden J, Zabaneh D, Pingault J-B, Rimfeld K, von Stumm S, et al. Phenome-wide analysis of genome-wide polygenic scores. Mol Psychiatry. 2016;(May):1–6.

50. McCoy TH, Pellegrini AM, Perlis RH. Using phenome-wide association to investigate the function of a schizophrenia risk locus at SLC39A8. Transl Psychiatry. 2019 Jan;9(1):45.

51. Martin J, Tilling K, Hubbard L, Stergiakouli E, Thapar A, Davey Smith G, et al. Association of Genetic Risk for Schizophrenia With Nonparticipation Over Time in a Population-Based Cohort Study. Am J Epidemiol. 2016 Jun;183(12):1149–58.

52. Taylor A, Jones H, Sallis H, Smith GD, Lawlor D, Davies N, et al. Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2018 May;dyy060.

53. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. Int J Epidemiol. 2018 Feb;47(1):226–35.

482 54. Fazel S, Danesh J. Serious mental disorder in 23 000 prisoners: a systematic review of 62
483 surveys. Lancet. 2002 Feb;359(9306):545–50.

484 55. Lehman AF, Cordray DS. Prevalence of alcohol, drug, and mental disorders among the
485 homeless: one more time. Contemporary Drug Problems. 1993;20(3):355–86.

486 56. Keyes KM, Westreich D. UK Biobank, big data, and the consequences of non-
487 representativeness. Lancet. 2019 Mar;393(10178):1297.

488 57. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of
489 Sociodemographic and Health-Related Characteristics of UK Biobank Participants With
490 Those of the General Population. Am J Epidemiol. 2017 Nov;186(9):1026–34.

491

492

493

494

Table 1. Psychiatric GWAS phenotypes included in the present study.

Phenotype	Measurement	Source	Sample Size
Schizophrenia	Dichotomous phenotype. Entirely clinician-rated assessment.	Pardiñas et al., 2018	N = 105,318 (40,675 cases & 64,643 controls)
Bipolar Disorder	Dichotomous phenotype. Entirely clinician-rated assessment.	Stahl et al., 2018	N = 51,710 (20,352 cases & 31,358 controls)
Major Depressive Disorder	Dichotomous phenotype. Combination of clinician- and self-rated assessment.	Wray et al., 2018	N = 480,359 (135,458 cases & 344,901 controls)
Depression	Continuous phenotype. Primarily self-rated assessment.	Okbay et al., 2016	N = 161,460
Irritability	Dichotomous phenotype. Entirely self-rated assessment.	Present study	N = 205,270
Mania	Continuous phenotype. Entirely self-rated assessment.	Present study	N = 208,315
Psychosis	Continuous phenotype. Combination of clinician- and self-rated assessment.	Present study	N = 124,952

495

496

497

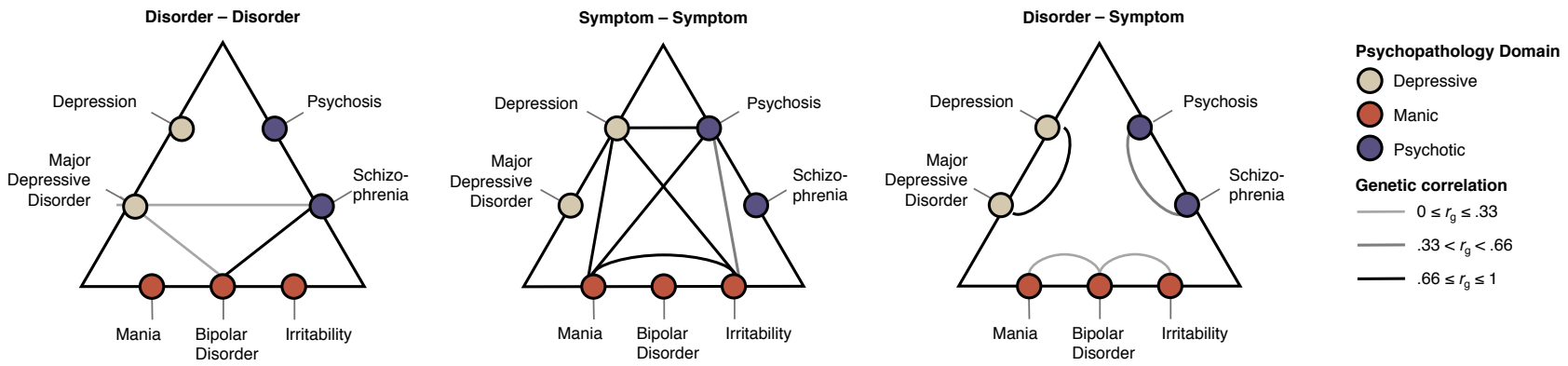


Figure 1. Genetic correlations among psychiatric disorders and symptom dimensions. Each triangle plot corresponds to a specific set of comparisons central to the present study (from left to right: disorder – disorder, symptom – symptom, and disorder – symptom). Phenotypes are colored according to psychopathology domain. All genetic correlations are statistically significant and the magnitude of the correlation is indicated by line thickness and darkness.

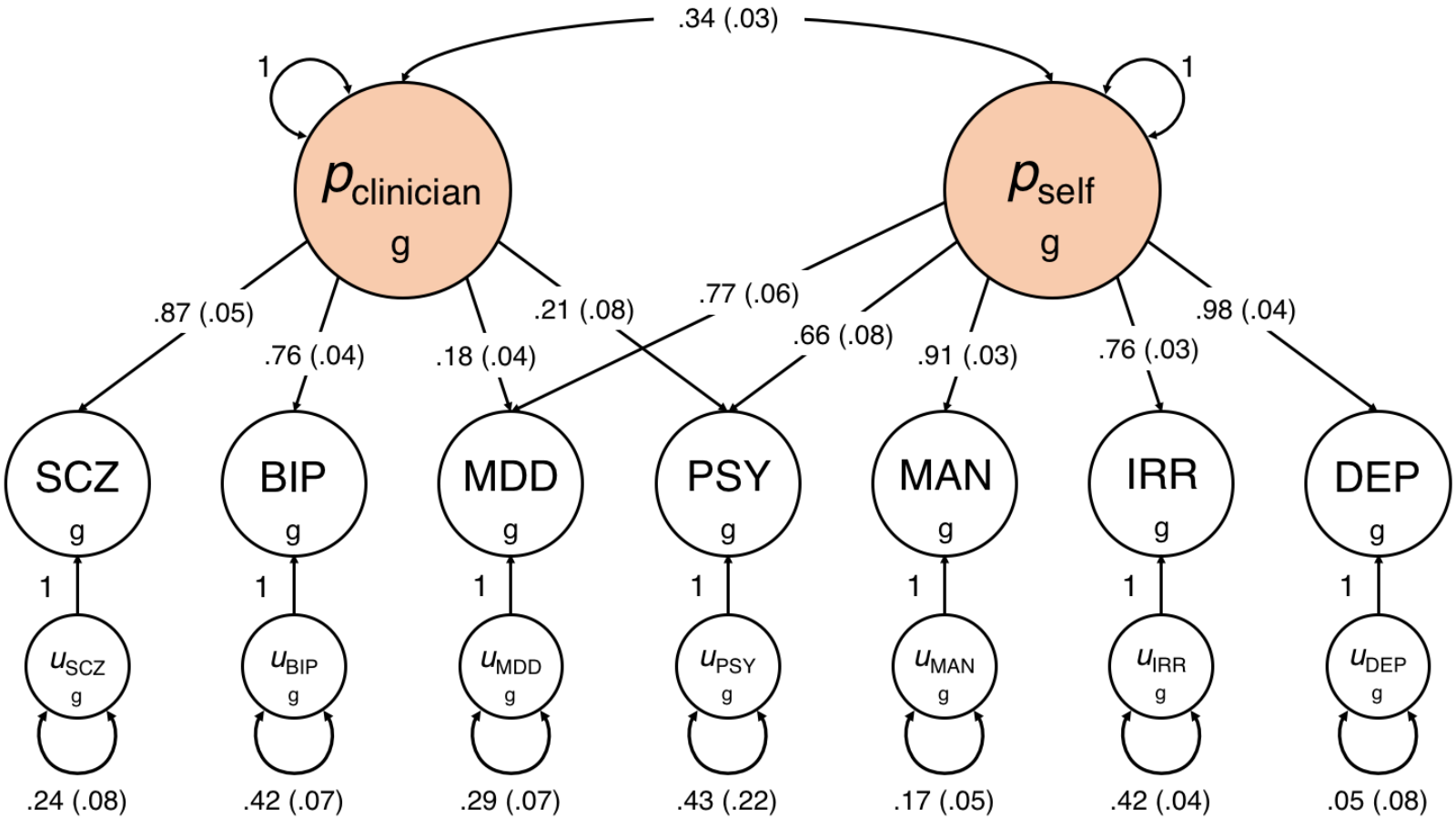
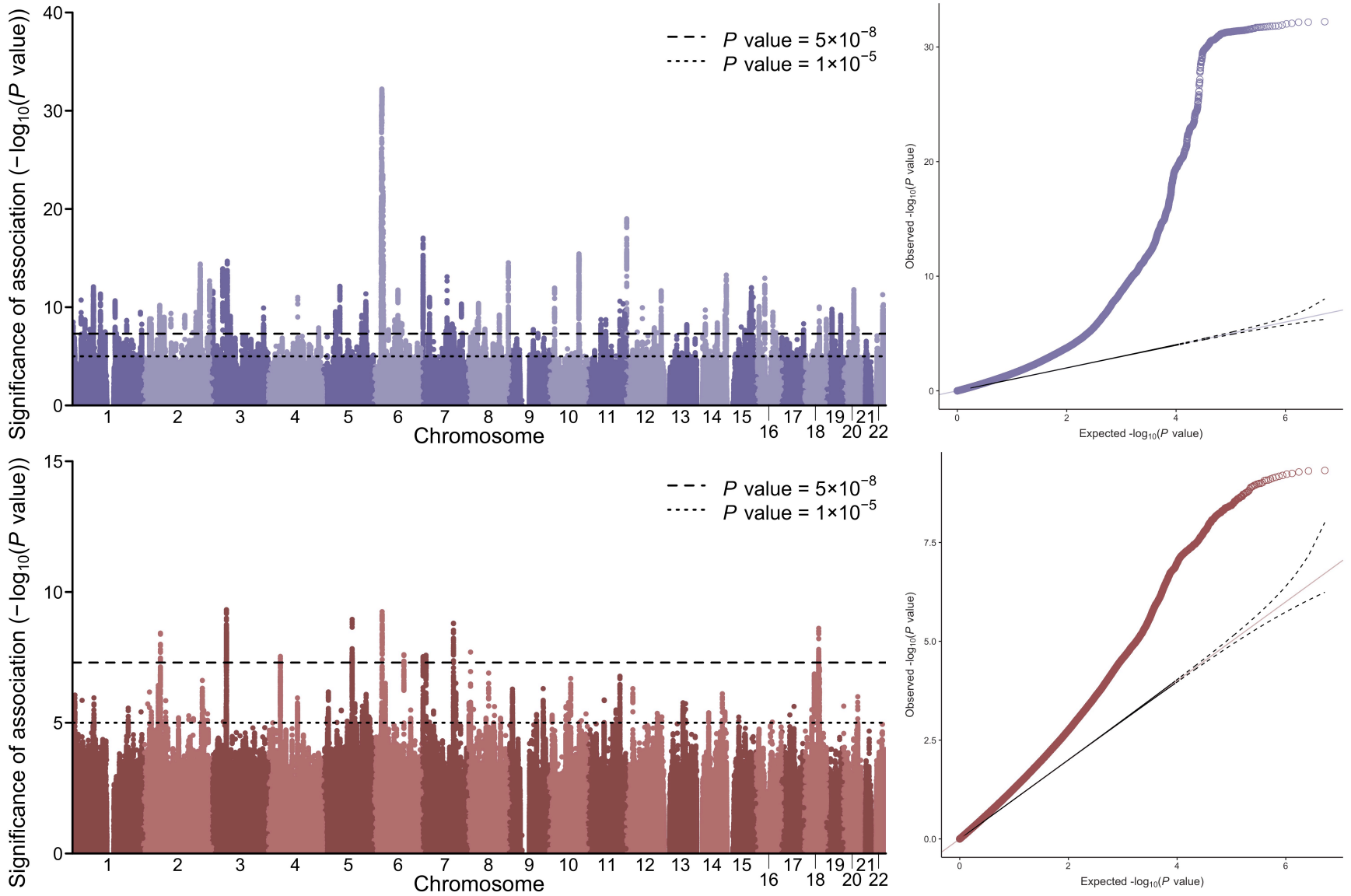
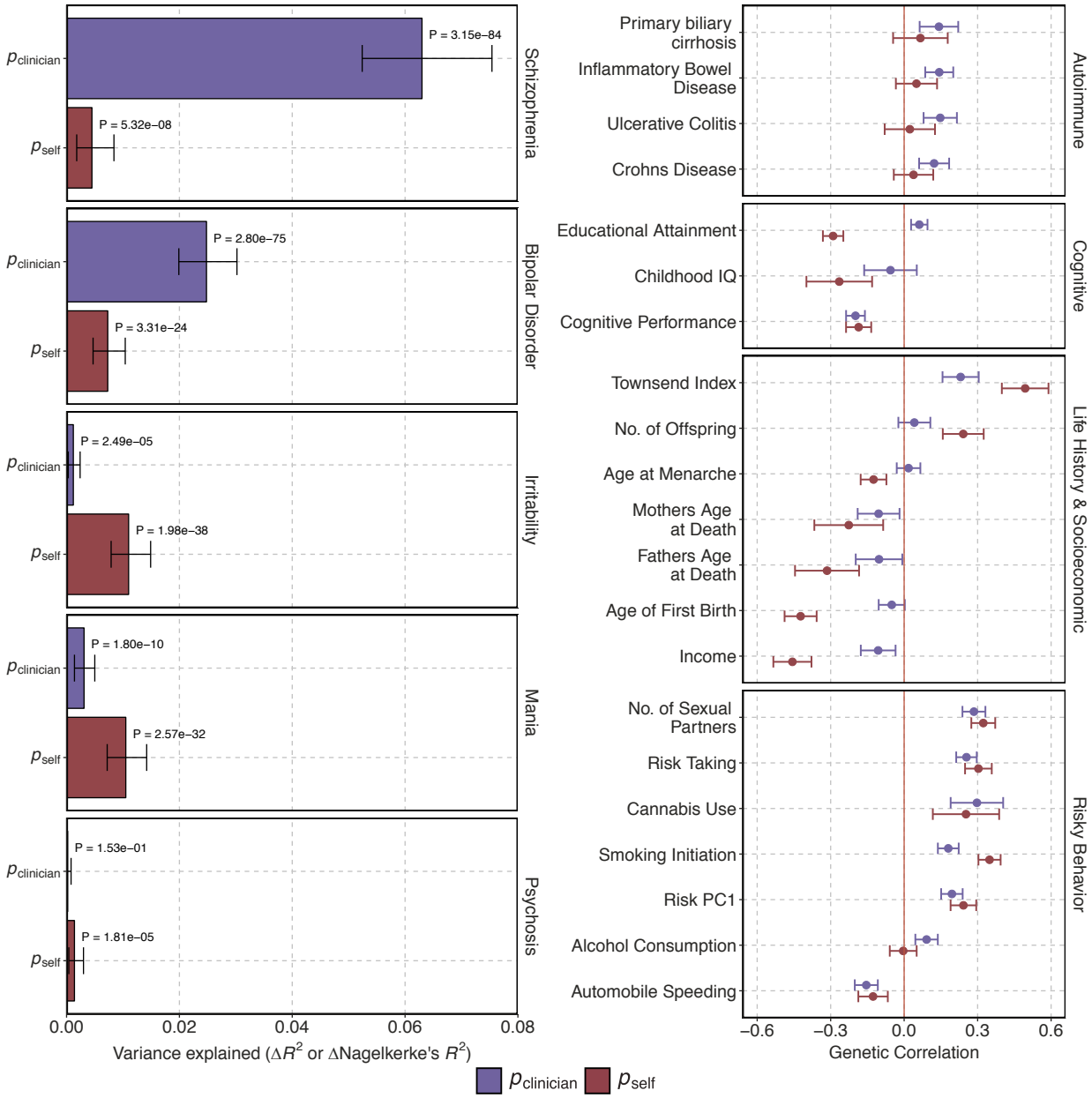


Figure 2. Final confirmatory factor model from Genomic SEM. Indicator loadings, residual variances, and the genetic correlation between latent factors in the final Genomic SEM model (i.e., Model D; $p_{clinician}$ and p_{self}). Note: SCZ = schizophrenia, BIP = bipolar disorder, MDD = major depressive disorder, PSY = psychosis, MAN = mania, IRR = irritability, DEP = depressive symptoms.


Significance of association (−log10(P value))
P value = 5×10−8
P value = 1×10−5
Chromosome
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Observed -log10(P value)
Expected -log10(P value)

509

Figure 3. Association results for $p_{clinician}$ and p_{self}. The top panels (blue) correspond to a Manhattan plot and a quantile-quantile plot for $p_{clinician}$. The bottom panels (red) correspond to a Manhattan plot and a quantile-quantile plot for p_{self}. In the Manhattan plots, the x-axis refers to chromosomal position, the y-axis refers to the significance on a −log10 scale, and the horizontal dashed line marks the threshold for genome-wide significance ($P = 5\times10^{-8}$). In the quantile-quantile plots, the x-axis refers to expected *P* value, while the y-axis refers to the observed *P* value.


Schizophrenia
Bipolar Disorder
Irritability
Mania
Psychosis
$p_{clinician}$
p_{self}
P = 3.15e−84
P = 5.32e−08
P = 2.80e−75
P = 3.31e−24
P = 2.49e−05
P = 1.98e−38
P = 1.80e−10
P = 2.57e−32
P = 1.53e−01
P = 1.81e−05
0.00
0.02
0.04
0.06
0.08
Variance explained (ΔR^2 or ΔNagelkerke's R^2)
Autoimmune
Primary biliary cirrhosis
Inflammatory Bowel Disease
Ulcerative Colitis
Crohns Disease
Cognitive
Educational Attainment
Childhood IQ
Cognitive Performance
Life History & Socioeconomic
Townsend Index
No. of Offspring
Age at Menarche
Mothers Age at Death
Fathers Age at Death
Age of First Birth
Income
Risky Behavior
No. of Sexual Partners
Risk Taking
Cannabis Use
Smoking Initiation
Risk PC1
Alcohol Consumption
Automobile Speeding
−0.6
−0.3
0.0
0.3
0.6
Genetic Correlation
$p_{clinician}$
p_{self}

516

Figure 4. Follow-up analyses for $p_{clinician}$ and p_{self}. In the leftmost panels, the predictive ability of $p_{clinician}$ and p_{self} polygenic scores in UKB holdout samples. In the rightmost panels, genetic correlations between *p* factors and phenotypes related to health, cognition, and socioeconomic status. Error bars represent 95% confidence intervals.