Isolating transdiagnostic effects reveals specific genetic profiles in psychiatric disorders.

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# Abstract

Evidence indicates a great degree of genetic overlap between psychiatric diagnoses. Accounting for these transdiagnostic effects can sharpen research on disorder-specific genetic architecture. Here we isolate genetic effects that are shared across 11 major psychiatric disorders (p factor) to gain further insight into genetic specificity and comorbidity over and above that contributed by the p factor, unique to each psychiatric disorder. After adjusting for transdiagnostic genetic effects, we identified novel SNP associations and some changes in enrichment patterns. We examined genetic correlations among adjusted psychiatric traits as well as relationships with other biobehavioural traits. The landscape of genetic associations between pairs of psychiatric disorders changed substantially, and their genetic correlations with biobehavioural traits showed greater specificity. Isolating transdiagnostic genetic effects across major psychiatric disorders provides a nuanced understanding of disorder-specific genetic architecture and may help guide diagnostic nomenclature and treatment research.

# Introduction

Genetic studies have challenged the current classification of psychiatric disorders as distinct categorical diagnoses by revealing overlaps in their genetic architectures 1. For instance, the first genome-wide association study (GWAS) of schizophrenia uncovered shared genetic loci between schizophrenia and bipolar disorder 2 despite their distinct categorization in diagnostic manuals (e.g., DSM-IV 3). Further research using Linkage Disequilibrium Score Regression (LDSC 4) highlighted significant genetic correlations across most psychiatric diagnoses 5-8, unlike other neurological disorders such as Parkinson’s and Alzheimer's disease, which remained genetically distinct 9. A recent LDSC analysis of 11 major psychiatric diagnoses found that the genetic correlation between schizophrenia and bipolar disorder was 0.68, and the average of 55 genetic correlations between 11 diagnoses was 0.28 10.

The positive genetic manifold between diagnoses is consistent with the idea of a general factor of psychopathology 11, called *p* 12. The p factor describes the propensity to developing all forms of psychopathologies 13, and reflects the comorbidities between psychiatric conditions that have been observed concurrently 14, across the lifespan 15,16, and even across generations 13,17. A p factor has also emerged from recent genetic and genomic studies 8,10,18. Shared genetic effects across different disorder dimensions were found to be stable over development, even when considering different measures and reporters 18. Capturing what cuts across diagnostic categories (i.e., a transdiagnostic approach) was found to be more effective in predicting functional and life outcomes than individual diagnoses 19.

Therefore, isolating p from major psychiatric disorders could better capture the specific genetic effects associated with each disorder and provide a more precise understanding of disorder-specific biology. Previous research that isolated transdiagnostic effects to investigate specificity revealed novel genetic profiles and biological pathways in neurodevelopmental disorders 20 and alcohol use disorder 21. In this study, we applied Genomic Structural Equation Modelling (Genomic SEM) 22 to isolate transdiagnostic genetic effects across 11 psychiatric disorders from genetic effects specific to each psychiatric condition. As shorthand, we refer to these disorder-specific genetic effects as *non-p* to describe residual genetic variance independent of genomically identified p. We used summary statistics from these non-p GWA analyses to identify novel single nucleotide polymorphism (SNP) associations, to map risk variants to genes and enrichment tissues, and to estimate SNP heritability. We estimated genetic correlations between the disorders beyond transdiagnostic effects, and their correlations with external biobehavioural traits. We hypothesized that non-p traits will provide us with novel insight into the genetic architecture of psychiatric disorders and their correlations, consequently informing research and practice into diagnostics and treatment.

# Results

## Isolating transdiagnostic genetic signal from 11 major psychiatric disorders

Following our preregistered analysis plan ([OSF pre-registration](https://osf.io/nq2wy?mode=&revisionId=&view_only=)), we proceeded in two stages: first, we modelled a genomic p factor using Genomic SEM, and second, we used the GWAS-by-subtraction 23 approach to isolate genetic effects associated with p from those contributing to each major psychiatric disorder that were not captured by p.

### Constructing a genomic p factor

We constructed a genomic p factor using the most recent summary statistics from GWAS of 11 major psychiatric disorders (Grotzinger et al., 2022 10 ; see Supplementary Table 1). First, a standard set of quality control (QC) filters (Methods) was applied to all GWAS summary statistics within Genomic SEM. These summary statistics were then used in a multivariable version of *LDSC* (Methods). Genetic correlations are presented in Supplementary Table 2. We found a positive manifold of genetic correlation (rG) among most disorders, with a mean rG of 0.29. Estimates ranged between -0.11 for the rG between obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) and 0.90 between anxiety and major depressive disorder (MDD).

To capture transdiagnostic genetic effects across all 11 disorders, we fitted a common factor model to the genetic covariance matrix. In this model, all disorders loaded on a single common factor (i.e., the p-factor; Fig. 1A). We ran a GWAS on this latent p factor and estimated individual SNP effects associated with p 22. Using LDSC, we estimated the SNP heritability for the p factor to be 9.9% (*h*2 = 0.099, s.e. = 0.004). Conventional ‘clumping’ applied with PLINK v1.9 24 identified 200 independent genome-wide significant lead SNPs (outside a 250-kb window or within a 250-kb window if LD *r*2 <0.1) (see Supplementary Figure 1).

### Isolating transdiagnostic genetic signals from each psychiatric disorder

We used GWAS-by-subtraction (Methods) to separate genetic effects associated with the previously constructed genomic p-factor from the genetic effects associated with each psychiatric disorder. This allowed us to identify genetic effects associated with each disorder independent of transdiagnostic genetic effects. Figure 1B provides a diagram of the GWAS-by-subtraction model using SCZ as an example. We repeated this procedure 11 times to isolate transdiagnostic genetic effects from each of the 11 major psychiatric disorders.

After applying a standard clumping algorithm (outside a 250-kb window, or within a 250-kb window if LD *r*2 <0.1), we identified genome-wide significant lead SNPs independent of p for schizophrenia (SCZ, 114 hits), bipolar disorder (BIP, 19 hits), attention-deficit /hyperactivity disorder (ADHD, 11 hits), anorexia nervosa (AN, 6 hits) and alcohol use (ALCH, 2 hits). No SNPs reached significance beyond the genome-wide significance threshold of p < 5 × 10−8 for major depressive disorder (MDD), anxiety (ANX), post-traumatic stress disorder (PTSD), autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD), and Tourette Syndrome (TS). Figures 1C-E show the Manhattan plots for SCZ, BIP and ADHD after accounting for genomic p. Supplementary Figures 2-9 show Manhattan plots for the remaining 8 psychiatric disorders after accounting for transdiagnostic genetic effects.

## Novel genetic variants associated with psychiatric disorders beyond transdiagnostic effects.

After accounting for the transdiagnostic genetic effects associated with p, we identified independent significant hits for five out of eleven GWASs. The largest number of independent hits was observed for the ‘non-p’ GWAS of schizophrenia (114, 17 of which were novel SNP associations that had not emerged as significant in the original GWAS), followed by BIP (19, 9 novel SNP associations), ADHD (11, 4 novel SNP associations), AN (6, 5 novel SNP associations) and ALCH (2). These newly detected SNP associations are presented in Supplementary Tables 4-8. Some of these SNP associations had been uncovered by GWAS of psychiatric disorders other than the 11 included in our model, or by GWAS of other traits (not psychiatric disorders), while others had not been reported in the previous literature. For example, focusing on schizophrenia, 4 out of the 17 novel SNP associations had been uncovered by previous genomic studies on schizophrenia 25-28, 6 had been reported as SNPs associated with physiological or psychological traits (i.e.; body mass index (BMI) 29 and intelligence 30), and 7 SNP associations had not been reported in the extant literature. After accounting for transdiagnostic effects, the novel SNP most significantly linked to schizophrenia was rs693906, p = 2.13E-13, located on chromosome 6, within the intron of the SLC44A4 gene, a gene that had been previously linked to schizophrenia in a Japanese sample 31. Novel SNP associations uncovered for the other four ‘non-p’ GWASs are presented in the Supplementary Notes and Supplementary Tables 5-8.

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**Figure 1.** **Isolating transdiagnostic genetic effects from 11 major psychiatric disorders.** **A.** ***Standardized results for the genomic p factor***. Each square indicates observed variables (i.e., the summary statistics for each of the 11 major psychiatric disorders) and circles represent latent variables that are statistically inferred from the data (i.e., genetic p-factor). One-headed arrows are standardized factor loadings, representing regression relations with the arrow pointing from the predictor variable to the outcome variable. Covariance relationships between variables are represented as two-headed arrows linking the variables. Residual variances of a variable are represented as a two-headed arrow connecting the variable to itself. SEs are shown in parentheses. ADHD = attention-deficit hyperactivity disorder; SCZ, schizophrenia; ASD, autism spectrum disorder; ANX, anxiety disorder; BIP, bipolar disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; ALCH, problematic alcohol use; TS, Tourette syndrome; OCD, obsessive-compulsive disorder; AN, anorexia nervosa; p, general psychopathology factor. **B. *Isolating transdiagnostic effects from each disorder using GWAS-by-subtraction.*** Panel B shows a schematic overview of how we applied GWAS-by-subtraction in this context, using SCZ as an example, to create a GWAS of a latent residual factor for SCZ. In the model, the GWAS summary statistics of the p-factor and SCZ are regressed on a latent factor (p) representing genetic variance shared across 11 disorders. SCZ was further regressed on a second latent factor representing the residual genetic variance in SCZ left over after regressing out variance related to p, i.e., non-p SCZ. The p SCZ and non-p SCZ factors are specified to be uncorrelated. These two latent variables, p SCZ and non-p SCZ, are then regressed on each SNP, iterating across all SNPs in the GWAS, yielding a GWAS of the latent constructs p and non-p SCZ. **C, D and E. *Manhattan plots for SCZ (C), BIP (D) and ADHD (E)*.** Plot of the -log10 (p-value) associated with the Wald test (two-sided) of βp for all SNPs ordered by chromosome and base position. Red diamonds indicate genome-wide significant independent hits (within a 250Kb window and r2 < .1) associations. **F and G.** ***SNP-based heritability******estimates*** before (on the liability scale) and after (on the observed scale) removing genetic effects shared with the latent p-factor. Error bars indicate standard errors.

## Mapping risk variants to genes and enrichment analysis beyond transdiagnostic effects

We used MAGMA 32 (see Methods) to evaluate the genetic effects of the 11 non-p GWASs on protein-coding genes. We performed gene-set analyses to identify biological pathways linked to genes associated with each major psychiatric disorder before and after accounting for p, and to analyse tissue type enrichment (Methods).The full results are reported in the Supplementary Notes and Supplementary Tables 9-17. We found that after accounting for transdiagnostic genetic effects, 316 genes were associated with SCZ, 72 genes were associated with BIP, 22 with ADHD, 28 with AN and 1 with ALCH. Only SCZ and BIP showed significant enriched gene sets after accounting for p. SCZ non-p was associated with enrichment in six gene-sets related to neuron system (Supplementary Table 10). BIP non-pwas significantly associated with enrichment in 5 gene-sets related to synaptic signalling (Supplementary Table 12).

We tested whether common variants in genes specifically expressed in 53 Genotype-Tissue Expression (GTEx) tissueswere enriched in their effects on psychiatric disorders (SCZ, BIP, ADHD, ALCH, AN) after accounting for transdiagnostic effects. Genes predominantly expressed in the brain cortex and other brain-specific tissues were enriched in SCZ, BIP, ADHD, and AN (Supplementary Notes, Supplementary Figures 14-19, and Supplementary Table 18-37). Enrichment patterns were overall consistent between psychiatric disorders before and after removing transdiagnostic signals, but there were some exceptions. First, brain development stages enrichment results showed that, for SCZ , the early-to-late prenatal stages were enriched before accounting for p, but no longer enriched after removing transdiagnostic effects. Late infancy remained the most enriched developmental stage for SCZ, showing the strongest associations (Supplementary Figure 11, Supplementary Table 19, 21). Second, for BIP developmental stage enrichment changed from young adulthood before accounting for p, to late infancy after accounting for transdiagnostic effects (Supplementary Figure 13, Supplementary Table 23, 25).

*SNP heritabilities for disorders independent of p*

We used LDSC implemented in Genomic SEM to estimate SNP-based heritability (h2) for the 11 disorders after partialing out the genetic variance associated with p. Figures 1F and 1G, and Supplementary Table 38 show the SNP-based h2 estimates for the 11 disorders (on the liability scale) and for the residual variance in each psychiatric disorder after accounting for the genetic effects associated with p (on the observed scale). In general, the pattern of SNP h2 remained similar before and after controlling for p. For example, the highest SNP h2 were observed for OCD and TS and the lowest estimates for ALCH and PTSD. However, genetic variance was reduced on average after controlling for p, a trend most apparent for MDD (7.1% to 1.6%) and ANX (21.8% to 8.6%). Genetic variance was also reduced for SCZ, BIP, ADHD, PTSD, and ALCH. Slight increases in SNP h2 were observed for ASD, OCD, AN, and TS.

## Removing transdiagnostic genetic effects significantly changed genetic relationships between psychiatric disorders.

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Figure 2 shows genetic correlations between the 11 psychiatric disorders before and after removing the genetic variance each had in common with p (see Supplementary Tables 2 and 39 for LDSC results for the corrected and uncorrected disorders). Overall, we observed significant changes in the genetic correlations between disorder pairs after removing transdiagnostic genetic effects, indicating greater genetic specificity. The average genetic correlation dropped from 0.29 to -0.02 after accounting for genomic p. However, changes in the relations between psychiatric disorders after accounting for transdiagnostic genetic effects were not homogeneous across all disorder pairs.

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**Figure 2| Genetic correlations between psychiatric disorders. A)** Genetic correlations between 11 major psychiatric disorders uncorrected for p. **b)** Genetic correlations between psychiatric disorders after removing the genetic variance each disorder shares with p. Correlations were estimated using LDSC within Genomic SEM.

For some disorders, genetic correlations remained substantial, even after accounting for transdiagnostic effects. For example, moderate to strong genetic correlations between ANX and MDD (rG = 0.68, SE = 0.08) and between SCZ and BIP (rG = 0.45, SE = 0.04) could still be observed. For other disorders, genetic associations were not significant after accounting for transdiagnostic genetic effects. This could be observed most notably for the otherwise strong correlation between PTSD and ANX (rG = 0.63, SE = 0.08), which was reduced to 0.11 (SE = 0.19) after removing the genetic variance they shared with p. Similarly, the moderate genetic correlation between ASD and ANX (rG = 0.36, SE = 0.05) dropped to 0.01 (SE = 0.10).

Another pattern of change was observed for the genetic correlations between OCD and ADHD and between TS and PTSD. For these disorder pairs, associations that were previously negative, but small or not significant, remained negative, but their effect size increased substantially. The genetic correlation between OCD and ADHD increased from -0.11 (SE = 0.06) to -0.44 (SE = 0.09), and the genetic correlation between TS and PTSD increased from -0.09 (SE = 0.10) to -0.36 (SE = 0.20). The most dramatic pattern of change emerged for the psychotic disorders of MDD, BIP and SCZ, in which genetic correlations switched from positive to negative after removing transdiagnostic genetic effects. For MDD and SCZ, the genetic correlation changed from 0.34 (SE = .03) to -0.82 (SE = 0.05). The change was similarly dramatic for the association between MDD and BIP, from 0.44 (SE = 0.03) to -0.64 (SE = 0.06).

The same pattern of genetic correlations was obtained when isolated transdiagnostic effects and obtained disorder-specific summary statistics using a common factor model (Supplementary Figures 23 and 24).

## Genetic architecture of the associations with external traits

In addition to removing transdiagnostic genetic effects from the relationships between psychiatric disorders, we also compared genetic correlations between each of the 11 psychiatric disorders – uncorrected and corrected for p – and 36 traits that are not psychiatric disorders (Methods). We focused on four broad categories of external traits: socio-demographic, anthropometric, health-related, and psychological traits. These correlations are shown in Supplementary Figures 20-22, with details in Supplementary Table 40. Figures 3 and 4 highlight some of these results. Figure 3 shows that the average genetic correlations for psychiatric disorders after controlling p were reduced, especially when considering health-related and psychological traits. This finding suggests that accounting for p removes some of the diffuse transdiagnostic effects of p, which extend far beyond psychiatric conditions. However, the average genetic associations with anthropometric and demographic traits were comparable before and after removing transdiagnostic genetic effects from psychiatric disorders.

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**Figure 3. Average genetic correlations between psychiatric disorders and categories of external traits.** The length of each bar represents the average genetic correlation between 11 major psychiatric disorders, before and after controlling for p, and four categories of external traits: psychological, health-related, socio-demographic and anthropometric after controlling for p. Genetic correlations were calculated using LDSC regression and are presented in Supplementary Table 40.

Figure 4 presents genetic correlations for the 11 psychiatric disorders uncorrected and corrected for p and psychological traits. Correlations between disorders uncorrected and corrected for p and most psychological traits differed significantly, as indicated by the red asterisks. In almost all cases, the genetic correlations were lower for the corrected than for the uncorrected psychiatric traits. Importantly, correlations with the same traits often appeared to be significantly different across major psychiatric disorders, such as self-rated health, sensitivity to environmental stress and tiredness. For example, consider sensitivity to environmental stress. Uncorrected for p, genetic correlations were significant and substantial between environmental stress and major psychiatric disorders, but corrected for p, these correlations were significantly lower and sometimes negligible: SCZ (0.19 vs -0.02), MDD (0.53 vs 0.20), BIP (0.17 vs. - 0.09), and ADHD (0. 18 vs. -0.06). A similar pattern of results was observed for several external traits that often co-occur with most psychiatric disorders, such as low subjective wellbeing, loneliness, tiredness and insomnia.

In other words, genetic effects associated with each major psychiatric disorder also include overlapping genetic variance associated with these transdiagnostic traits, such as sensitivity to environmental stress, which mask their specificity. Supplementary Figures 20-22 and Supplementary Table 40 present the genetic correlations between psychiatric disorders and all socio-demographic, anthropometric, health-related and psychological traits. As shown in Supplementary Figure 20 and Supplementary Table 40, similar results emerged for health-related traits. Genetic correlations between disorders corrected for p were generally lower than those uncorrected for p, often significantly lower. For example, self-reported poor health showed significant reductions for four disorders (ANX, BIP, MDD, SCZ); the age of smoking initiation yielded significant reductions for five disorders (ALC, ANX, BIP, MDD, SCZ); and the risk behaviour composite showed significant reductions for four disorders (ALC, ANX, MDD, SCZ).

Though most of the changes in correlations were reductions, there were some exceptions. For example, after accounting for p, the genetic correlation between BIP and educational attainment increased significantly. Other genetic correlations reversed after accounting for p. For example, the genetic correlation between BIP and loneliness changed from rG = 0.11 before accounting for p to rG = -0.21 after removing transdiagnostic effects, a similar change was also observed for the genetic correlations between BIP and Chronic Pain (from 0.08 to -0.12) and MDD and several cognitive traits (Intelligence (from -0.10 to 0.15), Executive Functions (from -0,18 to 0.25) and Noncognitive Skills (from -0.09 to 0.19)) and risk-taking behaviours (e.g., the correlation between MDD and Risk Tolerance changed from 0.14 to -0.23). Significant changes were also observed for the genetic correlations between ANX and Risk-Taking Behaviour (from 0.14 to -0.14), ANX and Risk Tolerance (from 0.07 to -0.27), AND SCZ and Chronic Pain (from 0.05 to -0.15). Removing transdiagnostic genetic effects from psychiatric disorders, particularly MDD, ANX, SCZ and BIP, resulted in divergent patterns of genetic associations with external biobehavioural traits.



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**Figure 4. Genetic correlations between 11 major psychiatric disorders and psychological traits.** The dots represent genetic correlations estimated using LDSC regression. Correlations with psychiatric disorders uncorrected for p (‘original’) are in blue, with psychiatric disorders corrected for p (‘non-p’) in green. Error bars represent 95% confidence intervals. Red asterisks indicate a statistically significant (FDR-corrected *P* < 0.05, two-tailed test) differences in the magnitude of the correlation with disorders uncorrected for p versus disorders corrected for p. Exact *P* values for all associations are reported in Supplementary Table 40. The FDR correction was applied based on all genetic correlations tested (including those reported in Supplementary Figures 20-22). Source GWASs are listed in Supplementary Table 41.

# DISCUSSION

We isolated transdiagnostic genetic effects across 11 major psychiatric disorders from genetic effects specific to each psychiatric condition. We uncovered differences in the genetic architecture of each disorder, identifying novel genome-wide significant SNP associations for four psychiatric conditions —schizophrenia, bipolar disorder, ADHD and anorexia nervosa— and specific changes in tissue enrichment. The greatest shift we observed, however, was in the genetic relationships between disorders, which changed substantially after considering transdiagnostic effects. Genetic effects associated with individual disorders beyond p also showed a greater degree of specificity in their genetic correlations with external biobehavioral traits, particularly health-related and psychological traits. By separating genetic influences into a shared and specific components, we provide novel insight into the genetic architecture, biology and comorbidity between psychiatric conditions that can inform diagnostic nomenclature and treatment research.

While our non-p GWA analyses revealed fewer genome-wide significant SNP associations than the GWA analyses uncorrected for p, they uncovered several novel trait-specific hits. For example, of the 17 novel SNP associations with SCZ, the top hit was an intronic SNP (rs693906) in a gene (SLC44A4) previously found to be associated with schizophrenia in a Japanese sample 31. Such novel non-p SNPs associations might provide new leads to uncover biological pathways specific to schizophrenia. Our analyses mapping risk variants to gene sets and tissue expression revealed specific changes in tissue enrichment beyond transdiagnostic effects, these were almost exclusively observed for SCZ and BIP. SNP heritabilities for most disorders remained stable when accounting for transdiagnostic effects, with the notable exceptions of MDD and ANX, which exhibited significant reductions in genetic variance.

We were particularly interested in investigating the genetic correlations between psychiatric disorders. We found that removing transdiagnostic genetic effects significantly changed genetic relationships between psychiatric conditions. While some genetic correlations showed a reduction in magnitude, the pattern of genetic correlations between several disorders shifted dramatically, highlighting discrepancies between diagnostic nosology and genetic structure of psychiatric disorders. For some pairs of disorders, positive genetic correlations disappeared entirely after correction for p, such as the genetic correlation between ANX and PTSD, indicating that their overlap is likely entirely captured by what cuts across all psychiatric diagnoses. Other pairs of disorders remained correlated positively after accounting for p, such as the genetic correlation between SCZ and BIP and between ANX and MDD, which suggests that only part of their overlap is shared with the other disorders included in our transdiagnostic model. It is important to remember that, although latent variables serve to summarize patterns of comorbidity or covariation among indicators, they are statistical constructs that depend on the indicators that are included in each model.

Other genetic correlations presented a more dramatic pattern of change. The genetic correlations between SCZ and MDD and between MDD and BIP switched from strongly positive to strongly negative after considering transdiagnostic effects. This negative correlation implies that, once transdiagnostic effects are accounted for, a genetic liability for one disorder conveys a lower genetic liability for the other disorder, this has the potential to inform diagnostic categorization and has far-reaching implications for future studies aimed at understanding biological causes and treatments for these disorders. Another major shift was observed for the slightly negative genetic correlation between OCD and ADHD, which became strongly negative after accounting for p. This suggests that their genetic overlap with p obscured the negative genetic relationship between these disorders. This finding is consistent with the current clinical perspective suggesting that OCD and ADHD lie at the opposite extremes of the impulsivity-compulsivity continuum 33,34.

Comparing genetic correlations between the 11 psychiatric disorders and external biobehavioural traits further indicated greater specificity for disorders corrected for p, especially for psychological and health-related traits. Though most of the changes in genetic correlations were reductions, there were some exceptions, with some correlations increasing, such as the genetic correlation between BIP and educational attainment, and other genetic correlations reversing, for example, BIP and loneliness, BIP and SCZ and Chronic Pain, and MDD and ANX and several cognitive traits and risk-taking behaviours. Removing transdiagnostic genetic effects from psychiatric disorders, particularly MDD, ANX, SCZ and BIP, resulted in divergent patterns of genetic associations with external biobehavioural traits. This is in line with extant research suggesting that, while genetic correlations among psychiatric disorders pointed to a general p-factor, a hierarchical factor model and a bifactor model of p offered limited biological insight and masked specific genetic associations between four disorders dimensions —neurodevelopmental, compulsive, psychotic and internalizing— and external biobehavioural traits 10.



Together, our findings highlight how isolating transdiagnostic genetic risk from major psychiatric disorders provides novel insight into disorder-specific genetic architecture and a more nuanced understanding of their comorbidities and co-occurrences with psychological and health-related traits. Consequently, our findings emphasize the significance of considering specificity as well as generality in psychiatric genetics. By demonstrating distinct genetic correlations and outcomes associated with psychiatric conditions independent of transdiagnostic effects, our findings pave the way for new avenues of research. One such application is the use of non-p summary statistics to create polygenic scores that index greater specificity in psychiatric disorders. For example, isolating transdiagnostic effects from psychiatric polygenic risk scores can lead to refined predictions of how biological risk for each disorder unfolds developmentally and can offer new avenues to investigate how genetic and environmental risk combine.

Our findings need to be interpreted in the context of their limitations. The most important limitation is that our research begins with case-control GWAS based on traditional diagnoses perfused with transdiagnostic effects. This points to the need for GWA research using phenotypes that correspond more closely to the genetic architecture of psychopathology. The origin of psychiatric nosology is historical rather than empirical; progress depends on more empirically derived dimensional approaches such as HiTop 35 and Rdoc 36.

Another limitation is that p is a statistical construct for which there is no consensus on what it is or how to measure it 37, which leaves non-p even further adrift from reality. However, similar accusations could be levelled at g, the general factor that emerges from diverse cognitive traits, but g is one of the most stable and predictive variables in the behavioural sciences 38. g is what diverse cognitive traits have in common and is not caused by any single physiological process, such as speed of neural conduction, nor is it defined by any single psychological process such as abstract reasoning. We embrace the possibility that p, like g, is not one thing – it is precisely what diverse traits have in common 39. We suggest that p will be similarly valuable for understanding general genetic influences, and that isolating the transdiagnostic effects captured by p will be useful in sharpening research on specific genetic influences, particularly in the context of developmental psychopathology and clinical epidemiological studies. Genetic effects that are disorder-specific might inform future research into causes and consequences of psychiatric conditions applying causal designs including mendelian randomization and longitudinal models 40,41.

A further limitation is related to our choice of modelling p as a common factor, given our interest in capturing transdiagnostic genetic effects that could index shared genetic liability across all 11 major psychiatric disorders. Although alternative models have been proposed 10,17,42 different statistical approaches to modelling p were found to lead to similar estimates 17. Relatedly, we allowed our indicators to load feely onto the common factor, as such, some disorders (e.g., ANX, MDD and PTSD) contributed more than others to the general factor (e.g., OCD and AN). A model in which all indicators are restricted to contribute the same amount of variance to the general factor would likely have led to different results, although arguably it would have provided a poorer account of transdiagnostic effects in psychopathology. It should also be noted that, while general factor models can fit psychopathological data, alternative explanations have been proposed, most notably network models 43.

Other limitations are general issues in GWA research. For example, the GWA studies that are the basis for this research are largely limited to individuals of European ancestry, so the results reported here might not generalize beyond this population 44,45. In addition, the contributing GWA studies are meta-analyses of different cohorts that may be subject to heterogeneity that cannot be fully quantified. Moreover, our research is limited by issues that could affect any GWA results, such as cross-trait assortative mating 46 and population stratification 47.

In conclusion, our results show that isolating transdiagnostic effects from major psychiatric disorders provides novel insight into disorder-specific genetic architecture a more precise understanding of the comorbidities and co-occurrences in psychopathology. Until better correspondence between psychiatric diagnoses and the genetic architecture of psychopathology is achieved, isolating p from diagnostic categories will sharpen genetic research by focusing on disorder-specific genetic effects.

# METHODS

The article is accompanied by Supplementary Information and the study followed a [preregistered analysis plan](https://osf.io/nq2wy).

## GWAS summary statistics

We used publicly available summary statistics from GWA studies of 11 major psychiatric disorders. Detailed information about the GWAS summary statistics, sample sizes and availability are provided in Supplementary Table 1. All summary statistics are based on samples of case-control European ancestry GWAS only. For details on the analysis protocol, we refer to the original publications.

## Genomic SEM

Genomic SEM 22 is a statistical framework that can model the shared and unique genetic architecture of complex traits by applying structural equation modelling principles to GWAS summary statistics. Genomic SEM is unbiased by sample overlap and imbalanced samples. Here, we used Genomic SEM to perform multivariate GWAS analysis of 11 major psychiatric disorders in order to construct a genomic p factor that captures transdiagnostic effects across all 11 disorders. Genomic SEM uses multivariable LD score regression to estimate the genetic covariance matrix and sampling covariance matrix . We applied quality control filters for this step using the defaults in Genomic SEM, including restricting SNPs to those present in HapMap3 with a minor allele frequency > 1% and information score > 0.9. The LD weights used for LDSC were calculated using the European subsample of the 1000 Genomes phase 3 project; excluding the major histocompatibility complex (MHC) due to complex LD structures in this region that can bias estimates. When calculating the liability scale heritability estimates for the uncorrected psychiatric disorders, we used the sum of effective sample sizes, and a sample prevalence of 0.5 to reflect that the corrected sample size already accounts for sample ascertainment. See Supplementary Notes for more details about processing summary statistics in Genomic SEM and calculating effective sample sizes. After the quality control steps, 3,746,806 SNPs were present across all 11 disorders.

We then fit a common factor model using genetic covariance and sampling covariance matrices to extract a latent genomic p factor, in which all disorders loaded on a single common factor. Supplementary Table 3 reports fit indices for the common factor model and standardized loadings.

## GWAS-by-subtraction

GWAS-by-subtraction 23 is a specific model within Genomic SEM that estimates, for each SNP, an effect on a specific trait that is independent of that SNP’s effect on another trait. The aim of our GWAS-by-subtraction analysis was to remove the genetic effects associated with the genomic p factor from the genetic effects associated with specific psychiatric disorders. Using SCZ as an example, summary statistics for the p factor (created in the previous step) and for SCZ were regressed on the two latent variables ‘p SCZ’ and ‘non-p SCZ’ (Fig. 1). The two latent variables were then regressed on each SNP, iterating across all SNPs in the GWAS. One path was fully mediated by p. The other path was independent of p and measured the SNP effects on SCZ independent of the genetic effects associated with the p factor. The same quality control filters were applied to summary statistics, as explained above. The effective sample size of the latent non-p factors was calculated following the method described by Demange et al. (2021) 23 (Supplementary Notes).

## Genetic correlations

We used LD score regression (LDSC) v1.0.1 4 to compute genetic correlations between each of the 11 psychiatric disorders –uncorrected and corrected for p– and 36 traits (Supplementary Table 40). The LD scores used were computed using 1,215,002 SNPs present in the HapMap 3 reference panel, excluding the MHC region on chromosome 6. The differences between genetic correlations before and after partialling out genetic effects associated with p factor were assessed using a two-stage method described in Coleman et al. (2020) 48. In this method, first, differences in genetic correlations were assessed using a two sample z-test, and significant differences (p < 0.05) were then compared using a block-jackknife correction. The results using the jackknife were then further corrected using the Benjamini-Hochberg False Discovery Rate (FDR) method to account for multiple testing.

## Independent significant SNPs and novel loci

To identify independent hits from the 11 Non-p GWAS, we applied a pruning approach using a window of 250 kb and an LD threshold of r2 < 0.1. This was done using the LD clumping function in Plink v1.9, with LD statistics obtained from the 1000 Genome Project.

Independent significant SNPs were considered novel under the following criteria: 1) they were not present in the original disorder GWAS; 2) they had been reported in GWAS of different traits; 3) they had not been reported in other GWAS listed in the GWAS Catalog database.

## Mapping of risk genes, enrichment and pathway analysis (MAGMA)

To follow up on the SNP-based association test for the non-p GWASs, we conducted downstream analysis using MAGMA within the FUMA framework (v1.5.6) 49. SNPs were assigned to genes based on their position (within 35kb upstream and 10kb downstream of each gene). Additionally, we performed genome-wide gene-based association tests using MAGMA. The gene-based test combines results from multiple SNPs within a gene to assess the association between the gene and the disorder, while accounting for linkage disequilibrium (LD) between SNPs. LD information was obtained from the 1000 Genomes Phase 3 EUR reference panel, and Bonferroni correction was applied to identify genes with genome-wide significance.

MAGMA also conducted gene-set analysis and gene property analysis for tissue specificity based on the gene-level p-values obtained from the gene-level analysis. Gene-set analyses assessed whether genes within an annotated set exhibited stronger associations with the disorder compared to other genes. Meanwhile, the tissue specificity test examined the relationship between tissue-specific gene expression profiles and disorder-gene associations. The gene-set analyses were performed using curated gene sets and Gene Ontology (GO) terms obtained from the Molecular Signatures Database v2023.1Hs. For the MAGMA gene property analysis, tissue expression profiles were obtained from GTEx v8 (comprising 54 tissue types) and BrainSpan (brain samples at 11 general developmental stages), available in FUMA. Gene sets and tissues were considered significant if the p-value was <0.05 after Bonferroni correction.

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# Conflict of Interest

The authors declare no conflict of interest.

# Contributions

E.K., W.L., R.P. and M.M. conceived and designed the study.; E.K. and W.L. analyzed the data with helpful contributions from M.M. and A.G.A.. E.K., W.L., R.P. and M.M. wrote the paper with helpful contributions from K.R., A.G.A., and T.C.E. All authors contributed to the interpretation of data, provided critical feedback on manuscript drafts, and approved the final draft.

# Code availability

Code will be available at <https://github.com/CoDEresearchlab> upon publication. Ahead of publication we will make the code available upon request.

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