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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Genomic SEM analyses were implemented using the publicly available code here for v0.5.0: https://github.com/GenomicSEM/GenomicSEM Factanal was conducted using publicly available code here within the stats R package for v3.6.2: https://www.rdocumentation.org/packages/stats/versions/3.6.2 MiXeR was conducted using publicly available code here for v1.3: https://github.com/precimed/mixer LAVA was conducted using publicly available code here for v.0.1.0: https://github.com/josefin-werme/LAVA CC-GWAS was conducted using publicly available code here for v0.1.0: https://github.com/wouterpeyrot/CCGWAS LDlink was conducted using publicly available code here for v1.4.0: https://cran.r-project.org/web/packages/LDlinkR/vignettes/LDlinkR.html ToppGene suite was conducted using publicly available code here for v0.1.0: https://toppgene.cchmc.org/ EWCE was conducted using publicly available code here for v.1.16.0: https://nathanskene.github.io/EWCE/ MAGMA was conducted using publicly available code here for v.2.0.15: https://neurogenomics.github.io/MAGMA_Celltyping/index.html

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Psychiatric disorder GWAS summary statistics for data from the PGC can be downloaded or requested here:
https://www.med.unc.edu/pgc/download-results/
Links to the LD-scores and reference panel data for GenomicSEM analyses can be found here: https://github.com/GenomicSEM/GenomicSEM/wiki
Links to the BaselineLD v2.2 annotations can be found here:
https://data.broadinstitute.org/alkesgroup/LDSCORE
Gene expression datasets from Brainspan can be found here:
https://brainspan.org/static/download.html

Multivariate GWAS summary statistics for the latent psychiatric factors in GenomicSEM, including the sensitivity GWAS results, are available at:
https://www.med.unc.edu/pgc/download-results/

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biological sex (as determined by the sex chromosomes) was used as a covariate in the original GWAS analyses for all included traits. All included GWAS summary statistics included both male and female subjects, with the exact split across males and females provided in the original papers describing this univariate GWAS data.
Reporting on race, ethnicity, or other socially relevant groupings	This study includes GWAS summary statistics for genetic ancestry groups that can be approximately described, based on genetic similarity to global reference panels, as reflecting European-like, East Asian-like, and African/African American-like genetic ancestries. The sample sizes are separately reported for each of these genetic ancestry groups in Extended Data Table 1.
Population characteristics	In order to achieve adequate power for GWAS analyses, the psychiatric disorders that are used as the primary data input in this paper include data from multiple cohorts, each with different population characteristics. The supplementary materials of the corresponding univariate GWAS papers include information on the different cohorts that went into their analyses. Our current manuscript reports sample sizes (case/control) and diagnosis for each disorder.
Recruitment	As described directly above, this study was not involved in recruitment of study participants. Rather, the individual cohorts that made-up the univariate GWAS for psychiatric disorders employed different recruitment strategies. This recruitment strategies ranged from volunteer basis, population-level surveys, and convenience sampling from hospital settings. As no single recruitment strategy was used for a psychiatric disorder this should ideally reduce bias induced by any one form of recruitment.
Ethics oversight	Primary data collection was not conducted for this study. As the data was used was already collected and deidentified, ethics oversight was not applicable.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The current study reflects the largest and most comprehensive cross-disorder psychiatric genetic analysis to-date. This study makes use of the largest psychiatric disorder GWAS currently available. Sample sizes for each of the included 14 disorders are provided in Table 1 of the main text.
Data exclusions	We employed strict quality control of the GWAS summary statistics prior to running analyses. These QC filters included removing strand ambiguous SNPs, restricting to SNPs with an imputation score (INFO) > 0.6 and with a minor allele frequency (MAF) > 1% when this information was available in the GWAS summary stats. Finally, we restrict to SNPs with a SNP-specific sum of the effective sample that is >

50% of the total sum of the effective sample or, when this SNP-specific information was not available, to SNPs for which > 50% of the cohorts contributed information, as indexed by the direction column in the GWAS summary stats. The MHC region was excluded from all summary statistics prior to the analysis.

Replication

We examined how genetic correlations in European-like genetic ancestry individuals compared to results from East Asian-like and African/ African American-like genetic ancestry individuals. The genetic correlation (rg) between major depression and schizophrenia in East Asian-like participants (rg = 0.45; SE = 0.09) was double that observed in European-like participants (rg = 0.22; SE = 0.04), though this discrepancy was previously shown to be driven by a single cohort of severe and recurrent major depression. Genetic correlations across disorders using African-like genetic ancestry GWAS did not produce any significant results due to lower power reflective of smaller participants sample sizes in these GWAS. Genetic correlations across genetic ancestry groups within a disorder were generally underpowered, but included a strong East Asian-like and European-like genetic correlation for schizophrenia.

Functional analyses using MAGMA, Expression-Weighted Cell Type Enrichment, and Stratified Genomic SEM replicated certain key findings, including the enrichment of excitatory neuron pathways for the Schizophrenia/Bipolar factor and oligodendrocyte biology for the Internalizing factor.

We also evaluated replication of results when utilizing more strictly ascertained samples of psychiatric cases. We find that the general pattern of results replicates for this ascertainment sensitivity analysis, with similar patterns of genetic correlations across disorders, multivariate genetic architecture, and genetic variants associated with the psychiatric factors.

Randomization

As this is a study of genetic risk for psychiatric disorders, and not a study of treatment effects as might be evaluated in a randomized control trial, randomization is not relevant as a study consideration. This is because participants cannot be randomized by the experimenter to have a psychiatric disorder or not.

Blinding

Blinding does not apply to this type of study design as the study participants are not randomly assigned to have a psychiatric disorder or not. In addition, there is no bias that can be introduced by the scientists running the genetic association analyses being aware of their psychiatric case status.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.