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Corresponding author(s): Nilanjan Chatterjee

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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	R: v 4.0.2 and 4.3.2
Data analysis	R: v 4.0.2 and 4.3.2 ASSET: v 2.20.0 LDSC: v 1.0.1 metaUSAT: v 1.17 fastASSET v 0.1.0: https://github.com/gqi/fastASSET

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

All data used in this paper are publicly available. Summary statistics from the GRASP repository are available for download at https://grasp.nhlbi.nih.gov/Overview.aspx. Other summary data are available through links provided by the original publication (see Supplementary Data 1 for references). Biobank Japan GWAS summary statistics are available at the National
Bioscience Database Center (NBDC) Human Database with the accession code hum0197 (https://humandbs.dbcls.jp/en/hum0197-v18). Functional genomic data can be accessed via links below. Source data are provided with this paper.

- GTEx Consortium: https://www.gtexportal.org/home/
- Roadmap Epigenomics Project: https://egg2.wustl.edu/roadmap/web_portal/index.html
- Neale lab UK Biobank GWAS: http://www.nealelab.is/uk-biobank
- JASPAR database for transcription factor binding profiles: http://jaspar.genereg.net/
- ABC model: https://www.engreitzlab.org/resources/
- Biobank Japan GWAS and European ancestry validation GWAS summary statistics: https://humandbs.dbcls.jp/en/hum0197-v18

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	The findings apply to both sexes. All data are publicly available and no consent was needed.
Reporting on race, ethnicity, or other socially relevant groupings	The main discovery data are primarily from individuals of European ancestry. A second dataset is from individuals of East Asian ancestry.
Population characteristics	See above.
Recruitment	No recruitment is needed for this study.
Ethics oversight	This study uses publicly available data. The approval of study protocol were obtained by the previous studies that collected the data.

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 study uses publicly available data hence no sample size calculation was performed. Sample size for GWAS ranges from 7,280 to 1.23 million. The number of GWAS summary-level datasets was determined by collecting all full summary statistics from the GRASP repository and apply QC filtering as described in Supplementary Figure 1. GRASP is a comprehensive repository for well-powered GWAS where many individual-trait associations were reported. Hence the number of datasets is sufficient for our analysis.
Data exclusions	For the primary analysis of European GWASs, we apply several filtering steps sequentially: 1) remove datasets in which the genetics variants do not have genome-wide coverage (genotyped by exome array, metabochip and immunochip); 2) remove datasets that only report p-values without direction of effect; 3) remove studies with small sample size: for continuous traits, we remove studies with sample size < 5,000; for binary traits, we remove studies with < 5,000 cases or < 5,000 controls; 4) remove studies where >25% individuals are of non-European ancestry; 5) remove duplicated traits: among the studies for the same trait, we keep the study with the largest sample size and discard the rest of them; 6) remove traits that are deterministic functions of other traits in our study, or other traits adjusted of covariates.
Replication	We attempted to validate the estimated degree of pleiotropy for both the European and East Asian datasets. (1) For the European ancestry data of GRASP and GWAS Consortia, we compared the estimated level of pleiotropy with that in UK Biobank. We observed a correlation of 0.43, a clear sign of replication. Since the two studies have very different numbers of traits, we were not able to obtain a higher correlation. (2) For the analysis of Biobank Japan data, we attempted to replicate the findings in European GWAS. The correlation between the estimated

	pleiotropy is 0.34, a sign of replication as well. Although the set of traits is largely the same for two ancestries, minor allele frequencies, linkage disequilibrium and genetic effects could be different. These differences prevented us from obtaining a higher correlation.
Randomization	Summary statistics are publicly available and from observational studies. No randomization was needed.
Blinding	The study only uses existing publicly available data from observational studies. No new experiments were conducted in this study, hence blinding was not applicable. Covariates were already controlled when the GWAS summary statistics were generated in the original studies. Typical covariates include age, sex, and genetic principal components. Therefore, additional covariate adjustment was not needed for our analysis.

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	n/a
Novel plant genotypes	n/a
Authentication	n/a