nature portfolio

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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	Data collection was performed by UK Biobank, as described by Bycroft, C. et al. (2018)
Data analysis	Custom codes were created using R version 3.644, which will be made publicly available in GitHub. Network and Pathway analyses were performed using g:Profiler, Cytoscape version 3.9.1 and DisGeNET.

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 UK Biobank data included in our analyses were accessed as part of our approved application #15255. Currently all data is available through UK Biobank Research Analysis Platform following an application process.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	All analyses were corrected for genetic-sex specific differences, where applicable.
Population characteristics	The UK Biobank (UKB) study is a prospective cohort comprising of approximately 500,000 participants (ages 40–69 years) with extensive genotypic and phenotypic data from consenting individuals. Details of the population can be found in the UK Biobank website.
Recruitment	Recruitment was performed by UK Biobank, as described by Bycroft, C. et al, 2018.
Ethics oversight	Ethics approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (11/NW/0382), as stated by Bycroft, C. et al. (2018)

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	We utilized 167,348 unrelated Caucasian participants with Whole-exome sequence data.
Data exclusions	Of the 200,643 samples with WES data that was released in November, 2021, individuals were excluded based on: consent withdrawal (n=11), call rates less than 99% (n=2), discordance between genetic and reported sex (n=18), a departure from putative ancestorial clusters based on the first two genetic principal components (n=3), assigned cluster membership to a continental population with less than 5,000 samples (n=12,765, of which, South Asian=3,395; African=3,168; Other=6,202), and 3rd degree or closer relatedness (n=14,156). In the remaining 173,688 individuals, an additional 6,340 were removed following QC of biomarker data. We focused on the 167,348 unrelated Caucasian participants.
Replication	Analyses was performed multiple times. The codes used to create results, statistical methods and the results were reviewed by several co-authors with subject-matter expertise.
Randomization	Correction for medication were were performed using exclusion of individuals or with correction factors, as described in the manuscript. We implemented residualisation of the traits based on age, sex and 20 PCs as the covariates.
Blinding	Blinding is not relevant to the study as it is not subjected to bias due to prior knowledge of the traits or genetic 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

Methods

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*