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	No software or code was involved in data collection. The data used is all directly available from the UK Biobank, as described in the paper.
Data analysis	This study used open-source software and codes, specifically R (v4.2.0; https://www.r-project.org/), glmnet (v4.1-4; https://github.com/cran/glmnet), clusterProfiler (v4.7.1.003; https://github.com/YuLab-SMU/clusterProfiler), Seurat (v4.1.4; https://satijalab.org/seurat), harmony (v0.1.0; https://github.com/immunogenomics/harmony), TwoSampleMR (v0.5.6; https://github.com/MRCIEU/TwoSampleMR), DEswan (v0.0.0.9001; https://github.com/lehallib/DEswan), and ggpubr (v0.6.0; https://github.com/cran/ggpubr).

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

The data used in our study were available from the UK Biobank with restrictions applied. The data used in this study were available in the UK Biobank under

application number 19542, and access to the UK Biobank data can be requested through a standard protocol via the website: https://www.ukbiobank.ac.uk/register-apply/. The single-cell transcriptomic data were acquired from GEO database (https://www.ncbi.nlm.nih.gov/geo/) with the accession number: GSE173731, GSE174367, and GSE213516.

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	We took sex into considerations in our study and our findings could apply to both male and female. Sex in the UK Biobank was determined based on self-reporting data via questionnaire, and all included participants gave written informed consent for sharing of individual-level data.
Reporting on race, ethnicity, or other socially relevant groupings	Ethic background (Field ID 21000) was used to define ethic background in this study.
Population characteristics	We included participants with both multimodal brain imaging data and plasma proteomics data (n = 4,696). The participants had a mean age of 63.16 years and comprised 53.6% females and 97.1% white ethnicities.
Recruitment	The participants included in the present study were from the UK Biobank, a large-scale prospective cohort with more than 500,000 community dwellers from 22 assessment centers throughout the United Kingdom between 2006 and 2010. The demographic characteristics, biological samples, and physical measurements of each participant were obtained at the recruitment, and all participants were registered with the UK National Health Service.
Ethics oversight	The UK Biobank obtained ethics approval from the North West Multicenter Research Ethical Committee and each participant has given written informed consent at the baseline.

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	No statistical methods were used to calculate the sample size. We screened the participants with both multimodal brain imaging data and plasma proteomics data (n = 4,696). The sample size was similar to the study reported in previous publication.
Data exclusions	Participants without multimodal brain imaging data or plasma proteomics data were excluded.
Replication	This was an observational study which did not involve experiments.
Randomization	Samples were randomly arranged by computing program into various batches of omics assay.
Blinding	Each sample was labeled with an numeric ID whose annotation was kept blinded during data collection and analyses.

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.