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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 purposes.
Data analysis	The following standard softwares were used for the analyses included in the current manuscript. PLINK (version 1.9); easy QC; METAL; FUMA; MAGMA; LDSC; COLOC (5.2.3); MR-MEGA (v 0.2); PRSice-2 (v 2.3.3); TwoSampleMR (v 0.5.7); Locuzoom

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 generated during this study are included in this published article and its supplementary information files. Individual cohort level summary datasets generated in this study can be made available upon request following the data access rules for the corresponding studies. We used publicly available data in this manuscript, including data from GTEx (https://gtexportal.org/home/) and publicly available GWAS summary statistics for Total hippocampal volume (https://

www.ebi.ac.uk/gwas/publications/30279459), Total brain volume (https://www.nature.com/articles/s41588-019-0516-6#Sec22), Alzheimer's disease (https://www.ebi.ac.uk/gwas/publications/30820047, https://www.ebi.ac.uk/gwas/publications/35379992), Parkinson's disease (https://www.ebi.ac.uk/gwas/studies/GCST90043734), White matter lesions (https://www.ebi.ac.uk/gwas/publications/33293549), T-tau (https://www.ebi.ac.uk/gwas/publications/35396452), amyotrophic lateral sclerosis (https://www.projectmine.com/research/download-data/), Huntington's disease (https://datadryad.org/stash/dataset/doi:10.5061%2Fdryad.5d4s2r8), Amyloid beta 40, 42 and ratio (https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/alz.12333)

Human research participants

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

Reporting on sex and gender	The female proportion varied from 0% in the Vietnam Era Twin Study of Aging (VESTA) cohort to 63% in the Cardiovascular Health Study (CHS) of European-American ancestry cohort. Moreover, CARDIA cohort of African-American ancestry had the lowest percentage of female participants (56.7%). No sex-stratified analyses have been performed in the current study.
Population characteristics	Our ancestry-specific GWAS meta-analysis of circulating levels of NfL was based on 11 different cohorts of European (N = 18532) and three cohorts of African-American ancestry (N = 1142), Supplementary Table 1. The Rotterdam Study and the Rhineland study were the major contributors (> 40%) to the total samples size. Participants of cohorts of European ancestry had diverse age ranges, varying from a mean age of 51 years (standard deviation [SD]= 3.2) in the Coronary Artery Risk Development in Young Adults (CARDIA) of European-American ancestry to a mean age of 85.3 years (SD = 6.7) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. The female proportion varied from 0% in the Vietnam Era Twin Study of Aging (VESTA) cohort to 63% in the Cardiovascular Health Study (CHS) of European-American ancestry cohort. Among the three cohorts of African-American ancestry, the Atherosclerosis Risk in Communities (ARIC) cohort contributed the largest number of participants, while the Cardiovascular Health Study (CHS) participants were older (mean = 76.3 years [SD = 4.93]) compared to the other two cohorts (mean ages of 61.5 [SD = 4.5] and 48.9 [SD = 3.5] years in the ARIC and CARDIA cohort, respectively). Moreover, CARDIA cohort of African-American ancestry had the lowest percentage of female participants (56.7%).
Recruitment	We have analyzed GWAS results from 11 different cohorts of European and African American Ancestry from CHARGE consortium. Details regarding recruitment of the participants for each study is available in Supplementary notes under Cohort Description section.
Ethics oversight	Prior to participation, each participant gave written, informed consent.

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 is based on 11 different cohorts of European (N = 18532) and 3 cohort of African American ancestry (N = 1142).
Data exclusions	Principal component analysis-based ethnic outliers, samples with missing values, and SNPs or samples that fail quality control were all subjected to the conventional exclusion criteria.
Replication	No replication analysis has been performed.
Randomization	NA
Blinding	NA

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