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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	We performed secondary data analysis for this study; no additional data was collected. Software for data collection is not applicable.
Data analysis	Sequence alignment and gene counting followed a published protocol including STAR (version 2.5.2b) alignment to the Ensembl (GRCh38 release 99) reference genome. Gene counts were obtained using the featureCounts function from the Subread package (v.2.0.0) Alignment metrics were calculated using Picard tools (version 2.18.27, http://broadinstitute.github.io/picard/). Quantile normalization of gene expression data was performed with the cqn R package (version 1.48.0) and was additionally normalized using the limma R package (version 3.60.4). Male and female samples were matched using the R package MatchIt (version 4.6.0). All statistical analyses were performed using R version 4.2.1, and all analysis packages used (limma, nlme, survival) are publicly available on Bioconductor or CRAN. We performed pre-ranked gene set enrichment analyses with the R package fgsea (version 1.26.0)86 on all tested autosomal and X-linked genes per sex, brain region, and outcome. Analyses were limited to Gene Ontology: Biological Process (C5)33, 34 terms of 15 to 500 genes. No custom software or code was created for this manuscript.

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 ROS/MAP data used in this study are accessible either online on the Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD) Knowledge Portal (https://adknowledgeportal.synapse.org/Explore/Programs/DetailsPage?Program=AMP-AD, syn3219045) or via the Rush Alzheimer's Disease Center Resource Sharing Hub (https://www.radc.rush.edu/).

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	Sex differences in AD are a focus of the study, thus sex was considered in the study. Sex was self-reported by participants, but was also additionally verified chromosomally due to the use of gene expression data from the X and Y chromosomes. The number of males and females were matched, thus our study includes 50% male participants and 50% female (total number of samples, n=767; male/female sample sizes are listed in Table 1). Source data is publicly available on the AMP-AD Knowledge Portal or via the Rush ADRC Sharing Hub.
Reporting on race, ethnicity, or other socially relevant groupings	Self-reported race was used to match male and female participants, but it was not a main focus of the rest of the study.
Population characteristics	Overall, the mean age at death of the entire sample was 88.3 years (Standard Deviation (SD)=6.5, Range=67.3-108.3), and the average number of annual follow-up visits prior to death was 7.4 (SD=4.9, Range=0-23). Most participants self-identified as non-Hispanic White (98%), and 26% of participants carried at least one copy of APOE-ε4.
Recruitment	Data were obtained from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP). These studies enrolled older adults free of dementia who agreed to annual clinical evaluations and brain donation at death.
Ethics oversight	The Rush Institutional Review Board (IRB) approved all protocols and the Vanderbilt University Medical Center IRB approved secondary analyses of existing 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	Sample sizes were predetermined by matching available data from female participants to male participants. Propensity score matching was utilized on scores based on on age of death, PMI, education, latency to death (i.e., difference between age of death and age at last cognitive visit), race, and APOEε4 allele count. We found that this sample size was appropriate given previous literature reports using the same data source.
Data exclusions	No data were excluded except where already missing (missing covariates or phenotypes).
Replication	Replication using additional brain tissue was not performed in this study. Current efforts to replicate these findings are underway using whole blood RNAseq data.
Randomization	Randomization is not relevant to the study. Participants were specifically categorized based on their sex.
Blinding	Blinding was not relevant to the study, no results were reliant on blinding nor was group allocation performed randomly.

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.