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Reporting Summary

Nature Research 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 Research 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.
Data analysis	All analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.6.2.

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Raw and analyzed de-identified data from the Mayo Clinic Study on Aging can be requested using the following link: https://ras-rdrs.mayo.edu/Request/IndexRequest. The request will be reviewed by the Mayo Clinic Study on Aging investigators and Mayo Clinic to verify whether the request is subject to any intellectual property or confidentiality obligations. A data sharing agreement must be obtained prior to release.

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 included all 1,329 Mayo Clinic Study on Aging participants with available plasma P-tau181 and P-tau217 assays.
Data exclusions	Only those with missing data in any of the models were excluded.
Replication	Several sensitivity analyses were done. For example, analyses were run with all participants and stratified by cognitive diagnoses and cutpoints were examined with and without co-morbidities. All data analyses were run multiple times for confirmation of findings and the data is freely available for qualified investigators for replication (see data availability statement). Attempts at replication were successful.
Randomization	The current study is an observational cohort study. Therefore, participants were not randomized
Blinding	All plasma assays were performed by individuals who were blinded to the clinical data and group assignment Clinical diagnoses were performed blinded to the plasma results (i.e., performed before the plasma assays were run) and all neuroimaging data.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	sSamples were diluted 1:2 and 50 uL of diluted sample was used for each replicate. The assay was performed on a streptavidin small spot plate using the Meso Scale Discovery platform. P-tau181 used Biotinylated-AT270 (mIgG1, 1 ug/mL, Thermo Scientific cat. MN1050) as the capture and P-tau217 used Biotinylated-IBA493 (anti-phosphorylated Thr217 tau monoclonal antibody developed by Lilly Research Laboratories , 0.5 ug/mLmIgG1) as the capture. In this study, both assays used SULFO-4G10-E2 (anti-tau monoclonal antibody developed by Lilly Research Laboratories, 0.02 ug/mL) as the detector. Each assay was calibrated using a unique synthetic P-tau peptide coupled with a polyethylene glycol linker to a second tau peptide matching amino acid 111-130 according to the Tau441 sequence numbering. With the exception of AT270, available from Thermo Scientific (MN1050), the antibodies used in this study were not commercial and do not have catalog numbers.
Validation	Both P-tau181 and P-tau217 levels were measured in duplicate on the MSD platform by electrochemiluminescence using proprietary assays developed by Lilly Research Laboratories as previously described and published in several papers. For example, as cited, see Mielke et al JAMA Neurology 2021 or other studies including Palmqvist et al. Nature Medicine 2021.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Detailed information is provided in Table 1 and the Methods and Results. Briefly, 1,329 Mayo Clinic Study of Aging participants were included. The median age (IQR; range) of the cohort was 73.2 (53.5, 81.3; 30.7, 97.9) years, 730 (54.9%) were male, and 26.6% had an APOE ε4 allele. There were 153 (11.5%) participants with a clinical diagnosis of MCI and 15

	(1.1%) with dementia (10 AD dementia, 2 Lewy body dementia, 1 other dementia, and 2 indeterminate). Of the 1,329 participants, 1,066 (80.2%) had a concurrent amyloid PET scan with the plasma P-tau measures. There were 495 (37.2%) participants with a concurrent tau PET scan, all of whom also had amyloid PET.
Recruitment	In 2004, Olmsted County residents between the ages of 70 and 89 were enumerated using the Rochester Epidemiology Project (REP) medical records-linkage system in an age- and sex-stratified random sampling design25. The study was extended to include those aged 50 and older in 2012, and to those 30 and older in 2015. The present analysis includes all participants with measures of both plasma P-tau181 and P-tau217. There are no differences between those with versus without plasma P-tau181 and P-tau217. However, those who participate in the MCSA tend to be healthier than those who do not. Given the associations between the plasma P-tau variables and co-morbidities, associations are likely conservative.
Ethics oversight	The study was approved by Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants.

Note that full information on the approval of the study protocol must also be provided in the manuscript.