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	LC-MS experiments were performed using nanoAcquity UPLC system (Waters, Mildford, MA) coupled to Orbitrap Eclipse mass spectrometer (Thermo Scientific, San Jose, CA).
Data analysis	MS transitions peaks were extracted and quantified using Xcalibur software version 3.0.63 (Thermo Scientific). Statistical analyses were conducted using R version 4.1.0. pROC package (v1.18.4) was used.

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 datasets generated and/or analyzed during the current study are available from the corresponding authors (K.H., R.J.B and O.H). Research participant privacy protection is necessary for controlled access. We will share datasets within the restrictions of IRB ethics approvals, upon reasonable request. Pseudonymized data

from the BioFINDER-2 will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation and decisions by the Ethical Review Board of Sweden and Region Skåne, which should be regulated in a material transfer agreement. The Knight ADRC data are available to qualified investigators who have a proposal approved by R.J.B. and an institutional committee (https://knightadrc.wustl.edu/Research/ResourceRequest.htm). The study must be approved by an institutional review board to ensure ethical research practices and investigators must agree to the terms and conditions of the data use agreement, which includes not distributing the data without permission. We will provide responses within a few days for requests.

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 and gender were self-identified.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were not identified in this study because of the policy in BioFINDER-2 study.
Population characteristics	Population characteristics are described in Table 1, Supplementary Data Table 1 and 2. In the pilot BioFINDER-2 cohort (n=108), participants were divided in cognitively unimpaired (CU) either Amyloid-negative or positive (CU- [n=57] and CU+ [n=4], respectively), mild cognitive impairment Amyloid-positive (MCI+) (n=10), and AD dementia Amyloid-positive (AD+) (n=37). In the pilot Knight ADRC cohort (n=55), participants were divided in CU- (n=15) and CU+ (n=14) with Clinical Dementia Rating (CDR)=0, very mild AD dementia (CDR=0.5) Amyloid-positive (n=18), or AD+ with CDR≥1 (n=8). In the BioFINDER-2 validation cohort (n=739), participants were divided in CU- (n=110), CU+ (n=198), MCI+ (n=169), AD+ (n=134), Parkinson's disease or Lewy Body dementia (n=18), progressive supranuclear palsy or corticobasal syndrome (n=6), vascular dementia (n=4), frontotemporal dementia (n=2), R406W MAPT mutation carriers (n=2), MCI without Amyloid-positive (MCI-) (n=86), and other neurodegenerative dementia (n=12).
Recruitment	BioFINDER-2 cohort included cognitively unimpaired participants (recruited as cognitively normal controls or as subjective cognitive decline [SCD] patients), patients with MCI, AD dementia patients and patients with a non-AD neurodegenerative disease. Participants were recruited at Skåne University Hospital and the Hospital of Ängelholm in Sweden. Details on recruitment, exclusion and inclusion criteria have been presented before (reference 11). The Knight ADRC cohort consisted of community-dwelling volunteers enrolled in studies of memory and aging at Washington University in St. Louis. Knight ADRC participants underwent the Clinical Dementia Rating (CDR) test. Individuals with a CDR of 0.5 or greater were considered to have a dementia syndrome and the probable aetiology of the dementia syndrome was formulated by clinicians based on clinical features in accordance with standard criteria and methods.
Ethics oversight	All participants in the Swedish BioFINDER-2 and the Knight ADRC cohorts gave written informed consent and ethical approvals were granted by the Regional Ethical Committee in Lund, Sweden and the Washington University Human Research Protection Office, respectively.

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 pre-determine sample size but our sample size is similar or larger to that used for similar studies. (e.g., Horie, K., et al. Nat Med 29, 1954-1963 (2023) and Barthelemy, N.R., et al. Nat Med 26, 398-407 (2020))
Data exclusions	No data points were excluded from analyses; outliers were not removed.
Replication	We replicated our key findings in two pilot cohorts (pilot BioFINDER-2 and pilot Knight ADRC) and a large validation cohort (BioFINDER-2 validation cohort).
Randomization	Samples were randomized by groups such as cognitively unimpaired participants, patients with MCI, AD dementia patients and patients with a non-AD neurodegenerative disease. All samples had a random code as an identifier and researchers who performed experiments were blinded towards the code when performing the analyses.
Blinding	All assays and data extraction steps were performed by operators blinded to any clinical or biomarker information.

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

Antibodies

Antibodies used	HJ32.11 antibody (generated by Dr. David Holtzman) was used. For the purification of eMTBR-tau243 in plasma, the HJ32.11 antibody was coupled to sepharose beads at 3 mg/gram, and the beads with 45 micro-gram HJ32.11 antibody was added per sample (1.4 mL plasma).
Validation	HJ32.11 was validated in the following study. Horie, K. et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. Nat Med 29, 1954–1963 (2023).

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	BioFINDER-2 (NCT03174938) Knight ADRC (N/A--the study is NOT a clinical trial)
Study protocol	BioFINDER-2 (NCT03174938, https://clinicaltrials.gov/ct2/show/NCT03174938) Knight ADRC (N/A--the study is NOT a clinical trial)
Data collection	Data was obtained from plasma collected from participants in the BioFINDER-2 cohort (NCT03174938) including cognitively unimpaired participants, patients with MCI, AD dementia patients and patients with a non-AD neurodegenerative disease. Participants in the Knight ADRC cohort were community-dwelling volunteers enrolled in studies of memory and aging.
Outcomes	Secondary outcome measures including the change on plasma tau biomarkers measured by mass spectrimetry were obtained in this study.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A