

Reporting Summary

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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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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.
Data analysis	Analyses were carried out using R (version 4.0.2, http://www.r-project.org/), MATLAB R2023b Update 7 (version 23.2.0.2515942, http://www.mathworks.com), VoxelStats (version 1.2, https://github.com/sulantha2006/VoxelStats), Python (version 3.12.3, https://www.python.org), and neuromaps (version 0.0.5, https://github.com/netneurolab/neuromaps).

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 from the TRIAD study used in the present work are not publicly available, as the information could compromise the participants' privacy. Thus, anonymized data will be made available from the corresponding author upon reasonable request from a qualified academic researcher for the purpose of replicating the

procedures and results presented in this article. Arrangements for data sharing are subject to standard data-sharing agreements, and further information can be found on the study's website (<https://triad.tnl-mcgill.com/>). The data from the WRAP study can be requested through an online submission process (<https://wrap.wisc.edu>). AHBA microarray data is openly available at (<http://www.brain-map.org>), and mRNA brain expression maps can be downloaded from www.meduniwien.ac.at/neuroimaging/mRNA.html.

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 used the term "sex" throughout the article. Sex was self-reported. Gender information was not collected. In the primary sample, 33 (32.7%) were males. In the secondary sample, 95 (37.8%) were males. We included sex as a covariate for adjustment in statistical models. In addition, we conducted exploratory analyses to assess sex differences in A β -glia relationships.

Reporting on race, ethnicity, or other socially relevant groupings

No ethnicity or race-based analysis was performed.

Population characteristics

The primary sample comprised 101 individuals (62 cognitively unimpaired and 39 cognitively impaired) from the TRIAD cohort who had complete PET data for A β ([18F]AZD4694) and TSPO ([11C]PBR28), as well as clinical assessments and plasma GFAP measurements. The mean (SD) age of participants was 71.9 (6.5) years, and 33 (32.7%) were men (see Table 1 and Supplementary Table 1 for complete demographic characteristics). The secondary sample was composed of 251 participants (214 cognitively unimpaired and 37 cognitively impaired) from the WRAP and TRIAD cohorts with available data for A β PET ([18F]AZD4694 or [11C]PiB), CSF sTREM2, and plasma GFAP. The mean (SD) age of participants was 67.2 (7.3) years, and 95 (37.8%) were men (see Supplementary Table 2 for detailed demographic characteristics).

Recruitment

For TRIAD, participants were recruited from the community or outpatients at the McGill University Research Centre for Studies in Aging through advertisements, printed materials, word of mouth, and referrals. Exclusion criteria encompassed inability to speak English or French, inadequate auditory and visual capacities for neuropsychological testing, contraindications for PET or MRI, recent head trauma or major surgery, inadequately treated conditions, current enrollment in other studies, or active substance abuse. For WRAP, dementia-free individuals from the community were recruited through advertisements, word of mouth, and memory clinics where a parent had been diagnosed or treated. Inclusion criteria comprised fluency in English, adequate visual and auditory acuity to complete neuropsychological assessments, and good overall health, with no medical conditions expected to affect study participation. Of note, TRIAD and WRAP participants are volunteers who were motivated to participate in a study about dementia, which might limit the generalizability of our findings due to self-selection bias.

Ethics oversight

The TRIAD study was approved by the Montreal Neurological Institute PET Working Committee and the Douglas Mental Health University Institute Research Ethics Board (IUSMD-16-60). The WRAP study was approved by the University of Wisconsin-Madison Institutional Review Board (2023-1522). All participants provided written informed consent, and they were compensated in accordance with the number of study procedures completed.

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

For the primary sample, we genotyped 606 individuals for the rs6971 SNP in the TSPO gene, with 314 identified as TSPO high-affinity binders. From those, we studied 101 individuals aged 50 years or older who had complete PET data for A β ([18F]AZD4694) and TSPO ([11C]PBR28), as well as clinical assessments and plasma GFAP measurements. All participants included in the primary sample were enrolled in the TRIAD study. This sample size is among the largest studies assessing TSPO PET data (Zou et al., 2020, PMID: 31698286; Pascoal et al., 2021, PMID: 34446931; De Picker et al., 2023, PMID: 37543251; Snellman et al., 2023, PMID: 37016464; Ferrari-Souza et al., 2023, PMID: 37018391; Rossano et al., 2024, PMID: 38298155). We further assessed a secondary sample of 251 individuals from the WRAP and TRIAD cohorts with available A β PET ([18F]AZD4694 or [11C]PiB), CSF sTREM2, and plasma GFAP. Sample sizes were based on data availability and, thus, no statistical methods were used to pre-determine sample sizes.

Data exclusions

A detailed description of participant selection for the primary sample – composed of individuals enrolled in the TRIAD study – is shown in Extended Data Fig. 1. We genotyped 606 individuals for the rs6971 polymorphism in the TSPO gene and excluded 54 low-affinity binders and 238 mixed-affinity binders. Of the 314 high-affinity binders, we excluded individuals lacking data for A β PET, TSPO PET, or plasma GFAP. We also excluded individuals diagnosed with non-AD neurological diseases, ADAD mutation carriers, and those under 50 years of age. For the secondary sample, participants without complete data for A β PET, CSF sTREM2, or plasma GFAP were excluded. Given that no WRAP participant was diagnosed with dementia, analyses were restricted to CU and MCI individuals to minimize inter-cohort differences;

accordingly, TRIAD participants with AD dementia were excluded. Similar to the criteria applied for the primary sample, individuals from the TRIAD cohort with non-AD neurological diseases, ADAD mutation carriers, and those under 50 years of age were also excluded. For both the primary and secondary samples, participants with A β PET, CSF sTREM2, plasma GFAP, or plasma p-tau217 values exceeding three standard deviations above the population mean were identified as outliers and removed from the analyses.

Replication	We used two independent biomarker-characterized cohorts (TRIAD and WRAP), divided into primary (n = 101) and secondary samples (n = 251). The replication across both samples using different biomarkers constitutes a major strength of this study, as it reinforces the robustness and enhances the generalizability of our results.
Randomization	The data for the present study were obtained from the TRIAD (https://triad.tnl-mcgill.com) and WRAP (https://wrap.wisc.edu) cohorts, which are observational studies of aging and dementia. No allocation in experimental groups is performed or required for studies such as the one proposed here. Therefore, randomization is not applicable to this study. Statistical analyses were controlled for potential confounders.
Blinding	The collection and processing of biomarkers were performed blindly for clinical diagnosis.

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	<i>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.</i>
Novel plant genotypes	<i>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.</i>
Authentication	<i>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, mosaicism, off-target gene editing) were examined.</i>