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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 for the current study.
Data analysis	FreeSurfer v7.1; R version 4.2.1 ("gamm4" v 0.2.6; "MatchIt" 4.4.0) All code underlying the statistical analyses will be made available at https://github.com/jamesmroe/yearsBeforeAB

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 individual-level data supporting the results of the current study may be available upon request, given appropriate ethical and data protection approvals. Different limitations on data access apply to different samples. Participants in LCBC have not consented to share their data publicly online. Requests for the raw data can be submitted to the relevant principal investigator of each contributing study. For LCBC, data are available on request to A.M.F. For BACS, data are

available on request to W.J.J. Contact details are provided in Supplementary Note 2. ADNI is available at https://adni.loni.usc.edu/data-samples/adni-data/#AccessData pending application approval and compliance with the data usage agreement.

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 was used as a covariate-of-no-interest in all statistical analyses. We did not perform any sex-specific or sex-stratified analyses as this was not a primary aim of this work. Information on sex but not gender was obtained at the time of data collection.
Reporting on race, ethnicity, or other socially relevant groupings	We did not use any socially constructed or socially relevant categorization variables in statistical analyses. The brain change estimation made use of data from all individuals with longitudinal follow-up data, regardless of race or ethnicity.
Population characteristics	Demographic information on each of the study samples is available in Supplementary Tables 1 and described in the Methods.
Recruitment	This manuscript made use of pre-collected MRI and amyloid PET datasets and the recruitment procedures for each contributing study have been thoroughly described previously. We briefly describe these in the Methods and refer to previous reports for a full description of recruitment procedures. LCBC and BACS participants received compensation.
Ethics oversight	All participants provided written informed consent, and each study was approved by the local institutional review boards for human research. LCBC studies were approved by the Regional Ethical Committee of South-East Norway (2017/653). For BACS, ethical approval was obtained from institutional review boards at the Lawrence Berkeley National Laboratory and the University of California, Berkeley. For ADNI, ethical approval was obtained by the ADNI investigators.

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	Both MRI and PET sample sizes were determined based on data availability. No analyses were performed to pre-determine sample sizes. We gathered as much longitudinal MRI data as we could from individuals aged >30 years in three cognitively healthy ageing cohorts. For ADNI, we used only the MRI observations from the scanner field strength with the most timepoints per-person (or 3T when equal) to mitigate bias from scanner changes over time. To help ensure reliable MRI change estimates, participants with <0.5 years of follow-up data were excluded. The total combined MRI sample initially comprised 4570 MRI scans from 1051 individuals From these, we used all available amyloid PET data to determine groups for amyloid PET-based analyses. The grouping was based on 1684 PET scans from 691 individuals. Exact grouping procedures are thoroughly described in the Results and Methods. The number of MRIs and PET scans from each cohort is described in the Methods. The converter group initially consisted of 77 individuals with 283 PET scans (2-7 timepoints) and a maximum of 487 MRI scans (2-14 timepoints). The Aβ− group initially consisted of 412 individuals with 954 Aβ PET scans (1-7 timepoints) and in total 1850 MRI scans (2-12 timepoints). One strong outlier in ADNI data was detected and removed from the MRI data; see SI Fig 26 and Data Exclusions) To examine brain structure before Aβ accumulation, we truncated each person's MRI series so that the last scan included occurred at least X years before their first Aβ+ scan (X = 1-10 years), or X years before their predicted age at amyloid positivity (X = 1-7 years). Using all available longitudinal MRI data, we then modelled cortical thickness trajectories across age with nonlinear mixed models. Thus, the exact MRI sample size varied across truncation cutoffs and analyses. Exact sample sizes, including total number of MRIs and N including the GAMM trajectory modeling, and total number of MRIs and N for each of the two amyloid PET groups in the GAMM trajectory modeling, are reported in tables in the Figures illustrating the results from every analysis. For amyloid PET analyses based on time to predicted Aβ-positivity, one converter was excluded as their centiloid slope over time was negative (despite their unambiguous Aβ+ status; SI Fig 24). For regional PET analyses, the number of PET scans was slightly reduced due to the requirement for quality-checked regional SUVRs (rather than only global amyloid measures; converters: 260 scans, N = 76 [77 minus the excluded converter]; Aβ−: 931 scans, N = 412). For MRI analyses based on time to predicted Aβ-positivity, we used all MRI data in the converter group (i.e., also those acquired after conversion; 477 MRI scans; N = 76 [removing 10 MRIs from the excluded converter])

Data exclusions	One strong outlier (SD = 7.8) in the brain change data of ADNI controls was identified and removed from all MRI analyses. The outlier was detected via the principal component (PC1) of absolute change across the top 50 brain features with accelerated change in Alzheimer's disease (see SI Fig 26). We removed this outlier from all MRI analyses due to unrealistic change values. The outlier was an Aβ- subject, but we did not test how their inclusion affected the results of the present paper. For amyloid PET analyses based on time to predicted Aβ-positivity, one converter was excluded as their centiloid slope over time was negative (despite their unambiguous Aβ+ status; SI Fig 24).
Replication	We replicated the main results that used the combined MRI data across the three cohorts (LCBC, BACS and ADNI cohorts) in analyses that used LCBC converter MRIs only (SI Fig. 21), and in analyses that used BACS and ADNI converter MRIs only (SI Fig. 17-18). These analyses excluded the converter MRIs from the other sample(s) from the GAMM trajectory modeling. The scarcity of longitudinal MRI data collected many years prior to longitudinal Aβ PET data did not permit full replication in an entirely independent dataset not already used in the main sample, also because we relied on GAMM trajectory modeling procedures specifically aimed at maximizing the robustness of subject-specific estimates by including as much longitudinal data as possible. The main results based on MRIs acquired 1-10 years before the first Aβ+ observation were replicated in a complementary sample using MRIs acquired exclusively in the years before Aβ+ conversion (1-7 years). To increase confidence in the results, we show our findings are robust across many analytic specifications, drawing influence from multiverse-style analyses that emphasize the consistency of statistical results across analysis variations. These sensitivity analyses are transparently reported and visualized in their entirety throughout the paper and supplements.
Randomization	Randomization is not applicable. The paper is based on retrospective MRI and PET data. Group allocation was based on Aβ PET status in longitudinal Aβ PET data. A total of 1,684 Aβ PET scans (691 individuals, 1–7 time points each) were used to define two groups: those who converted from Aβ− to Aβ+, and those who remained Aβ− across all scans.
Blinding	Blinding is not applicable. The paper is based on retrospective MRI and PET data (see above)

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.*

Magnetic resonance imaging

Experimental design

Design type	T1-weighted anatomical scans Aβ PET scans ([18F]flutemetamol, [11C]Pittsburgh compound-B, [18F] florbetaben (FBB),

[18F] florbetapir)

Design specifications: NA

Behavioral performance measures: NA

Acquisition

Imaging type(s): Structural MRI

Field strength: 1.5T & 3T

Sequence & imaging parameters:

Structural MRIs for the LCBC cohort were acquired across the following scanners and acquisition parameters:
Avanto Siemens 1.5T; TR: 2400 ms, TE: 3.79 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240 × 240 mm, 160 slices.
Skyra Siemens 3T; TR: 2300 ms, TE: 2.98 ms, TI: 850 ms, flip angle: 8°, slice thickness: 1 mm, FoV: 256 × 256 mm, 176 slices.
Prisma Siemens 3T; TR: 2400 ms, TE: 2.22 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 0.8 mm, FoV: 240 × 256 mm, 208 slices, iPat = 2.

Structural MRIs for ADNI were acquired at ADNI-GO, ADNI-2 and ADNI-3 sites with 1.5T and 3T MRI scanners using 3D MP-RAGE or IR-SPGR T1-weighted sequences, as described online (https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/mri-scanner-protocols/).

Structural MRIs for BACS were collected on either a 1.5 T MRI scanner at Lawrence Berkeley National Laboratory (LBNL) or a 3T MRI scanner at UC Berkeley using 3D MP-RAGE T1-weighted sequences.

Area of acquisition: Whole brain

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software: Cortical and subcortical reconstruction was performed with FreeSurfer's longitudinal pipeline (v7.1.0)

Normalization: Normalization template = subject-specific unbiased within-subject anatomical average ("base" image). Normalization process = timepoints are aligned and normalized relative to this base, enhancing consistency and measurement precision. Base creation: Rigid (6 DOF), robust template. Talairach registration: Affine (12 DOF). Intensity normalization: mri_normalize using WM.

Normalization template: Talairach

Noise and artifact removal: mri_normalize used to correct for bias fields, primarily by standardizing white matter intensity. In the longitudinal analyses the base template guides normalization to make correction consistent across time. No explicit motion correction is performed within FreeSurfer itself, but mri_robust_template used for base creation is resilient to moderate motion, using outlier rejection and robust averaging. WM and GM priors from the base help stabilize segmentation across time. Surface placement is also initialized from the base, reducing variability.

Volume censoring: NA

Statistical modeling & inference

Model type and settings:

Generalized Additive Mixed Models (GAMMs) of age, adjusting for sex, scanner field strength, cohort, and intracranial volume (ICV; Methods) on the 70 cortical thickness measures (knots = 8). Random intercepts and slopes were included to estimate individual-level deviations in cortical thickness level and rate of change relative to the sample average. We ran comparable GAMMs omitting the random slope term to estimate the intercept of cortical thickness (intercept-only models), and alternative GAMMs with a tensor-product interaction between mean age and time from mean age (T2 models) to better separate within-person change from age-related differences.

We calculated the difference between age at each MRI in the converter group and their age at first Aβ+ scan observation, or predicted age on crossing the sample-specific Aβ+ threshold, then artificially truncated their longitudinal MRI series, ensuring the last MRI used to estimate brain change and structure was acquired at least X years prior to either observed or predicted Aβ positivity (X = 1-10 years [observed]; X = 1-7 years [predicted]). At each cutoff, we discarded those with fewer than two remaining timepoints, and entered the truncated MRI series from converters into the GAMMs, together with rest of the longitudinal MRI data. In sensitivity analyses, at each cutoff we matched the Aβ− group to converters based on mean age, follow-up time, and number of timepoints. Full details for all main, sensitivity, and additional analyses are reported in the main text.

Effect(s) tested: We used the GAMM-derived random effects (slopes or intercepts) at each cutoff as response variable in linear models with group (converters vs Aβ−) as the main predictor, adjusting for mean age, sex, cohort, number of timepoints, and follow-up time (i.e., time between first and last MRI), based on the data included at each cutoff. We repeated these with additional

adjustment for quantitative Aβ levels. Full details for all main, sensitivity, and additional analyses are reported in the main text.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s): We extracted and modelled 70 bilateral measures of cortical thickness from the Desikan-Killiany (DK) atlas (68 regional + 2 global hemispheric measures of mean cortical thickness).

Statistic type for inference (See Eklund et al. 2016): FDR-corrected ROI analyses

Correction: FDR-correction was applied within each map to adjust for multiple comparisons (70 tests), and p(FDR)<.05 was considered significant. Because statistical power varied considerably across time cutoffs and analyses, parcels that reached FDR-significance at any cutoff were considered significant at less-powered cutoffs at p<.05 (uncorrected).

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis