

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	Data used in this study were obtained from publicly available databases:UK Biobank (application ID: 89757)Alzheimer's Disease Neuroimaging Initiative (ADNI)Parkinson's Progression Markers Initiative (PPMI) No software was used for data collection.
Data analysis	Data analysis was conducted using the following software and custom code:Python 3.10 with PyTorch 2.0, MONAI 1.2, NumPy 1.24, scikit-learn 1.3, and SciPy 1.11Custom deep learning models (3D Vision Transformer) were implemented using PyTorch; full code will be made available upon request or deposited at [GitHub/Zenodo] upon publication.Statistical analysis was performed using R 4.3.1, packages including survival, splines, and ggplot2.

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](#)

Data used in this study were obtained from the following publicly available datasets: UK Biobank (access granted under application number 89757, <https://www.ukbiobank.ac.uk>) Alzheimer's Disease Neuroimaging Initiative (ADNI) (<http://adni.loni.usc.edu>) Parkinson's Progression Markers Initiative (PPMI) (<https://www.ppmi-info.org>) All datasets require institutional approval and data use agreements. Restrictions apply to the availability of these data, which were used under license for the current study and are not publicly redistributable. Qualified researchers can apply for data access through the respective project websites.

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 (biological attribute) was recorded in all datasets (UK Biobank, ADNI, PPMI), and sex-disaggregated analyses were performed. Sex was determined by self-report (UKB) or recorded at enrollment (ADNI, PPMI). Where appropriate, analyses were stratified or adjusted for sex.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity information was not used in this study. The primary covariates included age, sex, and clinical diagnosis. No socially constructed grouping variables were included or analyzed. The analysis did not aim to assess disparities or group-based effects.
Population characteristics	The study included adult participants across a wide age range from three large-scale cohorts (UK Biobank: general population; ADNI: individuals across the Alzheimer's disease spectrum; PPMI: Parkinson's disease and prodromal subjects). Detailed age, sex, and diagnostic composition are provided in Supplementary Tables 1-4 All participants were diagnosed or categorized according to the respective study protocols.
Recruitment	Participants were recruited under the original cohort protocols for UK Biobank, ADNI, and PPMI. Data used in this study were secondarily accessed under institutional approval and relevant data use agreements. Recruitment procedures, inclusion/exclusion criteria, and consent processes are publicly available through the respective study documentation.
Ethics oversight	Ethical approval for the use of UK Biobank data was obtained under application number 89757. Access to ADNI and PPMI data was granted through formal data access requests. All contributing institutions received ethics approval, and informed consent was obtained for data collection. This study only used de-identified, previously collected 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 determined based on the available number of participants with T1-weighted MRI scans in each dataset (UK Biobank: n=42,904; ADNI: n=1,402; PPMI: n=1,182). No formal a priori power analysis was conducted, but these sample sizes are consistent with or exceed those used in comparable neuroimaging studies. Sample size adequacy was further supported by the stable performance of the model across internal and external validations.
Data exclusions	Participants were excluded if they lacked T1-weighted MRI data or had imaging artifacts based on predefined quality control criteria. In UK Biobank, only individuals of genetically confirmed White British ancestry were included to minimize population stratification bias (final n=38,967). Exclusion criteria were established prior to analysis and documented in the Methods and Supplementary Figure 1.
Replication	Model generalizability and robustness were assessed via external validation on two independent datasets (ADNI and PPMI). Findings were consistently reproduced across cohorts and diagnostic groups using baseline T1-weighted MRI scans. Detailed replication procedures and outcomes are described in the Methods and Results sections.
Randomization	As this is an observational study using pre-existing datasets, random assignment was not applicable. However, participants were stratified by diagnosis and dataset for training, validation, and testing purposes. Cross-validation and cohort-specific evaluations were used to control for

potential biases.

Blinding

Blinding was not applicable as the analysis used de-identified data from publicly available repositories. No experimental intervention or group allocation by investigators occurred. Data labels (e.g., diagnosis) were accessed only after preprocessing to avoid leakage.

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

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	Not applicable. This study did not involve a prospective interventional clinical trial requiring registration.
Study protocol	This study used previously collected data from three established observational cohorts: UK Biobank (application ID: 89757), the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the Parkinson's Progression Markers Initiative (PPMI). Study protocols and eligibility criteria are publicly available on the respective cohort websites.
Data collection	Data were collected by the original cohort studies prior to this research. UK Biobank: Baseline T1-weighted MRI scans and clinical data were collected between 2014 and 2020 across multiple imaging centers in the UK. ADNI: MRI data and diagnostic information were collected from 2003 onward at over 50 sites in North America. PPMI: MRI and clinical assessments were collected from 2010 onward across international sites. This study accessed the data through formal data access agreements and did not involve new data collection.
Outcomes	The primary outcome was brain age predicted from T1-weighted MRI using a deep learning model. Secondary outcomes included brain age gap (BAG), defined as the difference between predicted and chronological age, and its association with clinical diagnoses. Outcome measures were pre-defined and assessed through regression analysis, stratification, and survival modeling as detailed in the Methods section.

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>

Magnetic resonance imaging

Experimental design

Design type	Structural MRI (T1-weighted); not applicable to task-based or resting-state fMRI design paradigms.
Design specifications	Not applicable. This study used structural T1-weighted MRI data without block or trial-based task design.

Behavioral performance measures Not applicable. No behavioral tasks or performance metrics were recorded during structural MRI acquisition.

Acquisition

Imaging type(s) Structural (T1-weighted)

Field strength 3 Tesla for UK Biobank and most ADNI/PPMI sites; ADNI and PPMI also include 3 Tesla scans.

Sequence & imaging parameters T1-weighted 3D MPRAGE sequences were used across cohorts. Typical parameters: TR $\approx$ 2000–2300 ms TE $\approx$ 2.0–2.9 ms Flip angle $\approx$ 8–9° Slice thickness = 1 mm Field of view $\approx$ 256 mm $\times$ 256 mm Matrix size = 256 $\times$ 256 Isotropic voxel resolution = 1 mm³ Detailed protocol variations across acquisition sites were harmonized through standardized preprocessing pipelines.

Area of acquisition Whole-brain acquisition

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software FMRIB Software Library (FSL), version 6.0.5. For ADNI and PPMI cohorts, preprocessing included anatomical reorientation, cropping, bias field correction, brain extraction using BET, and linear and nonlinear registration to MNI152 space. For UK Biobank, preprocessed images were used directly as provided by the UKB imaging team.

Normalization All T1-weighted images were registered to MNI152 standard space. UK Biobank images used affine registration; ADNI and PPMI images were normalized using linear and nonlinear transformations with six degrees of freedom via FSL.

Normalization template MNI152 (Montreal Neurological Institute, 1 mm³ isotropic resolution)

Noise and artifact removal Basic quality control was applied. Non-brain tissues were removed using FSL's BET. Bias field correction was performed without prior segmentation. No physiological noise correction (e.g., cardiac or respiratory signals) was applicable due to the structural nature of the data.

Volume censoring Not applicable. The study used single-volume structural T1-weighted MRI; no time series data were involved.

Statistical modeling & inference

Model type and settings Predictive modeling was conducted using a 3D Vision Transformer (3D-ViT) trained on T1-weighted structural MRI data for brain age estimation. Statistical analyses were performed at the subject level, including linear regression (OLS), restricted cubic spline (RCS) modeling, Cox proportional hazards models, and group comparisons (e.g., t-tests, Kruskal–Wallis tests). All regression models included covariates such as age, sex, BMI, smoking, and alcohol consumption. Five-fold cross-validation was used during model training to optimize performance and prevent overfitting. Missing data were handled via listwise deletion and multiple imputation (MICE).

Effect(s) tested The primary effect tested was the association between brain age gap (BAG: predicted age – chronological age) and various outcomes including: Cognitive performance across 8 domains Incidence of neurological, psychiatric, and neurodegenerative disorders All-cause mortality risk Interaction effects between lifestyle score categories and BAG Effects were tested via regression-based comparisons, spline-based non-linear modeling, survival analysis (hazard ratios), and stratified subgroup comparisons.

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

Statistic type for inference All statistical inference was conducted at the subject level using brain-age-derived variables (no voxel-wise or cluster-wise inference). Regression coefficients (β), hazard ratios (HRs), confidence intervals (CIs), and test statistics (t-values, p-values) were reported for inferential analysis.

(See [Eklund et al. 2016](#))

Correction Multiple comparisons across cognitive and clinical outcomes were corrected using the Benjamini–Hochberg false discovery rate (FDR) method. Post-hoc tests following Kruskal–Wallis tests were corrected using Dunn's test with multiple comparison adjustment. Nonlinear spline models were optimized using AIC criteria to avoid overfitting.

Models & analysis

n/a Involved in the study

☒ ☐ Functional and/or effective connectivity

☒ ☐ Graph analysis

☐ ☒ Multivariate modeling or predictive analysis

Multivariate modeling and predictive analysis A 3D Vision Transformer (3D-ViT) model was trained on T1-weighted structural MRI scans for whole-brain age prediction. The model input consisted of MRI volumes resized to 128 $\times$ 128 $\times$ 128 voxels. Each volume was divided into 512 non-overlapping 3D patches of size 16 $\times$ 16 $\times$ 16, which were embedded via linear transformation and positional encoding. These embeddings were processed through 3 layers of multi-head self-attention transformer encoders. A sum-pooling operation followed by a multilayer perceptron (MLP)

head (Linear → GELU → Linear → GELU → Linear) was used to generate the final age prediction. Feature extraction was performed end-to-end within the model; no external dimensionality reduction or ROI selection was applied. The model was trained using the Adam optimizer (learning rate = 2.0×10^{-5} , 200 epochs, early stopping after 10 epochs of no improvement) and evaluated using mean absolute error (MAE), mean squared error (MSE), Pearson correlation (r), and coefficient of determination (R^2). Five-fold cross-validation was used within the UK Biobank training set ($n = 31,452$). Model performance was further validated on external cohorts from ADNI and PPMI.