

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 (<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	Proteomic measurements were outsourced to the vendor; SomaLogic Inc, Boulder CO. Cohort data was derived from the MESA and ARIC Study using R.
Data analysis	All analyses were performed using R version 4.4.2 and SAS 9.4. Figure 1 was created using BioRender.

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 included in this paper and the supplement is available on reasonable request, or on public database such BioLINCC. Pre-existing data access policies for each of the parent cohort studies (ARIC and MESA) specify that research data requests can be submitted to each steering committee; where it will be reviewed for confidentiality and intellectual properties.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	Number of female and male participants are reported for both cohorts. Sex specific analyses were performed.
Population characteristics	Population characteristics are reported in detail in table 2 and supplementary tables S3-7.
Recruitment	Participant recruitment and inclusion in the study are reported in methods and figures S1A and B, S2, and S3.
Ethics oversight	The study was approved by each cohort's site's institutional review board, and written informed consent was signed by all participants (or proxies, when required).

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](https://www.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	We used the total sample available in both ARIC and MESA. Exclusion and inclusion detail is available in Figures S1, 2, and 3 and Table S3-7.
Data exclusions	ARIC: We included 11,758 participants with information on cognitive function and protein measurements at Visit 2 (midlife) and 4,934 participants at Visit 5 (late life) (Figures S1A & 1B) to train midlife and late-life PACs and analyze their association with incident dementia. For cognitive function, we included 5,123 participants at Visit 5 (late-life) who had available information on both cognitive function and proteins (Figure S2). There were 4,783 participants with protein data at Visit 2 (midlife) and cognitive function data at Visit 5 (Figure S2). MESA: We included 4,057 participants with protein measurements at Exam 1 and cognitive function information at Exam 5 and 5,829 participants with both protein measurements and information on dementia status (Figures S3).
Replication	We validated and replicated in the proteomic clocks and the associations with cognitive function and dementia incidence in MESA cohort, a prospective cohort including ethnically diverse participants identifying as Black, White, Asian, and Hispanic.
Randomization	Randomization was not applicable to our study design.
Blinding	Blinding was not applicable to our study design

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

Methods

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