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Reporting Summary

Nature Research 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 Research 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	Participating study-specific data collection information is provided in the supplementary methods and supplementary table
Data analysis	EasyQC, METAL, GCTA-COJO, MR-MEGA, MAGMA, LD-score regression, MTAG, Metafor package in R, GCTA-GSMR, RadialMR, MR-CAUSE, FUMA, VEGAS2, VEGAS2Pathway, COSMIC, TWAS-Fusion, COLOC R package, STEAP, S-LDSC, H-MAGMA, GREP, Trans-Phar, REGENIE

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Summary statistics for the GWAS meta-analyses on PVS burden will be deposited in a public repository and made available by the time of publication. All other data supporting the findings of this study are available either within the article, the supplementary information and supplementary data files, or from the authors upon reasonable request.

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	We conducted a multi-ancestry genome-wide association (GWAS) of perivascular space burden (PVS) in 40,095 participants. See Methods (page 28-29), Supplementary Table 1 and Supplementary Methods (pages 3-10) for more information about the samples.
Data exclusions	Participants were excluded from the analysis if they had co-morbidities modifying the measurement of the phenotype (stroke at time of MRI and brain tumor or other condition that may bias PVS measurement), missing covariates (Supplementary Table 1). Genotyped or imputed variants were excluded if they failed quality control filters described in the Methods (pages 28-29).
Replication	We used a two-stage study design, stage 1 included all the CHARGE cohorts (N=4,543), then we replicated the genome-wide significant associations in the independant UKB sample (N=28,500). In stage 2 we conducted a combined meta-analysis of CHARGE and UKB cohorts.
Randomization	We did not allocate participants into experimental groups. However we did conduct Mendelian randomization analyses based on genetic associations in the study population (described in the Methods).
Blinding	Not relevant for the present study design (strictly speaking PVS burden was measured blinded to the genotypes and vice versa).

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	A total of 40,095 participants (38,871 Europeans, 717 Hispanics, 339 East-Asians and 168 African-Americans) were included in this study, comprising 51.7% women and 66.7% hypertensives. Mean age was 66.3±8.6 years. Detailed population characteristics by study and phenotype definitions can be found in the Supplementary Methods and in Supplementary Table 1.
Recruitment	All participating studies had population-based recruitment strategies. Details can be found in the Supplementary Methods.
Ethics oversight	Study protocols were approved for all studies by the appropriate boards at their respective institutions. Details can be found in the Supplementary Methods.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Magnetic resonance imaging

Experimental design

Design type	Population-based brain imaging study.

Design specifications	The recruitment strategy for each cohort studies is described in the Supplementary Methods.
Behavioral performance measures	There are no behavioral performance measures in this study.

Acquisition

Imaging type(s)	Brain MRI with T1-, T2-weighted, FLAIR and proton density sequences images. Study-specific information is described in Supplementary Methods (section 1 and 2).
Field strength	1.5 and 3.0 Tesla.
Sequence & imaging parameters	Study-specific sequence and imaging parameters information is described in the Supplementary Methods (Section 2).
Area of acquisition	Brain.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Study-specific information is described in the Supplementary Methods (Section 1 and 2).
Normalization	Study-specific information is described in the Supplementary Methods (Section 1 and 2).
Normalization template	Study-specific information is described in the Supplementary Methods (Section 1 and 2).
Noise and artifact removal	Study-specific information is described in the Supplementary Methods (Section 1 and 2).
Volume censoring	Study-specific information is described in the Supplementary Methods (Section 1 and 2).

Statistical modeling & inference

Model type and settings	Detailed information on the models tested are provided in the Methods (page 26-39).
Effect(s) tested	Association of genetic variants with perivascular space burden in white matter, basal ganglia and hippoampus.

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

Statistic type for inference (See Eklund et al. 2016)	Non relevant for this study.
Correction	Bonferroni

Models & analysis

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