


Machine learning in Alzheimer's disease genetics

Received: 26 July 2024

Accepted: 24 June 2025

Published online: 22 July 2025

 Check for updates

A list of authors and their affiliations appears at the end of the paper

Traditional statistical approaches have advanced our understanding of the genetics of complex diseases, yet are limited to linear additive models. Here we applied machine learning (ML) to genome-wide data from 41,686 individuals in the largest European consortium on Alzheimer's disease (AD) to investigate the effectiveness of various ML algorithms in replicating known findings, discovering novel loci, and predicting individuals at risk. We utilised Gradient Boosting Machines (GBMs), biological pathway-informed Neural Networks (NNs), and Model-based Multifactor Dimensionality Reduction (MB-MDR) models. ML approaches successfully captured all genome-wide significant genetic variants identified in the training set and 22% of associations from larger meta-analyses. They highlight 6 novel loci which replicate in an external dataset, including variants which map to *ARHGAP25*, *LY6H*, *COG7*, *SOD1* and *ZNF597*. They further identify novel association in *AP4E1*, refining the genetic landscape of the known *SPPL2A* locus. Our results demonstrate that machine learning methods can achieve predictive performance comparable to classical approaches in genetic epidemiology and have the potential to uncover novel loci that remain undetected by traditional GWAS. These insights provide a complementary avenue for advancing the understanding of AD genetics.

Genome-wide association studies (GWAS) have enabled huge progress in identifying variants associated with the risk of developing Alzheimer's disease (AD)¹. Polygenic risk scores (PRS) based on these variants have greatly improved prediction of disease status². However, inherent to GWAS and PRS are the assumptions that variants are independent predictors, linearly associated with the outcome, and therefore combine additively within and between loci³, with no interactions occurring between variants, or between genes and other risk factors. While such simplifying genetic assumptions have proved fruitful across a range of diseases and disorders^{4,5}, they are at odds with biological evidence in AD that disease heterogeneity and responses from cells such as microglia are dependent on *APOE* status^{6–9}. Further, there is genetic evidence suggesting that different variants are associated with the disease depending on *APOE* status^{10–13} and age at diagnosis or assessment^{14–16}. As GWAS sample size increases and PRS approach limits on predictive performance, alternative modelling approaches

are essential to maximise discoveries from existing data and enable a deeper understanding of AD genetics.

The confluence of increasingly large genetic data¹⁷, readily available computational resources, and mature methodologies presents a key opportunity for addressing this at scale by applying flexible data-driven machine learning (ML) models. Several studies have applied ML to the genetics of brain disorders and have been recently summarised^{18,19}. Previous ML attempts have been impacted by high risk of bias²⁰ and population stratification²¹, while AD studies in particular have been hampered by low sample size¹⁸, leaving a gap for comprehensive, large-scale studies that rigorously apply ML to genome-wide data. We conducted the largest genome-wide ML study in AD to date, marking a pivotal moment in the field. Our study presents a reproducible, bias-aware approach for ML model development, validation, and confounder adjustment. We trained three of the most prominent approaches in the field to compare predictive accuracy and uncover

✉ e-mail: kristel.vansteen@uliege.be; cornelia.vanduijn@ndph.ox.ac.uk; EscottPriceV@cardiff.ac.uk

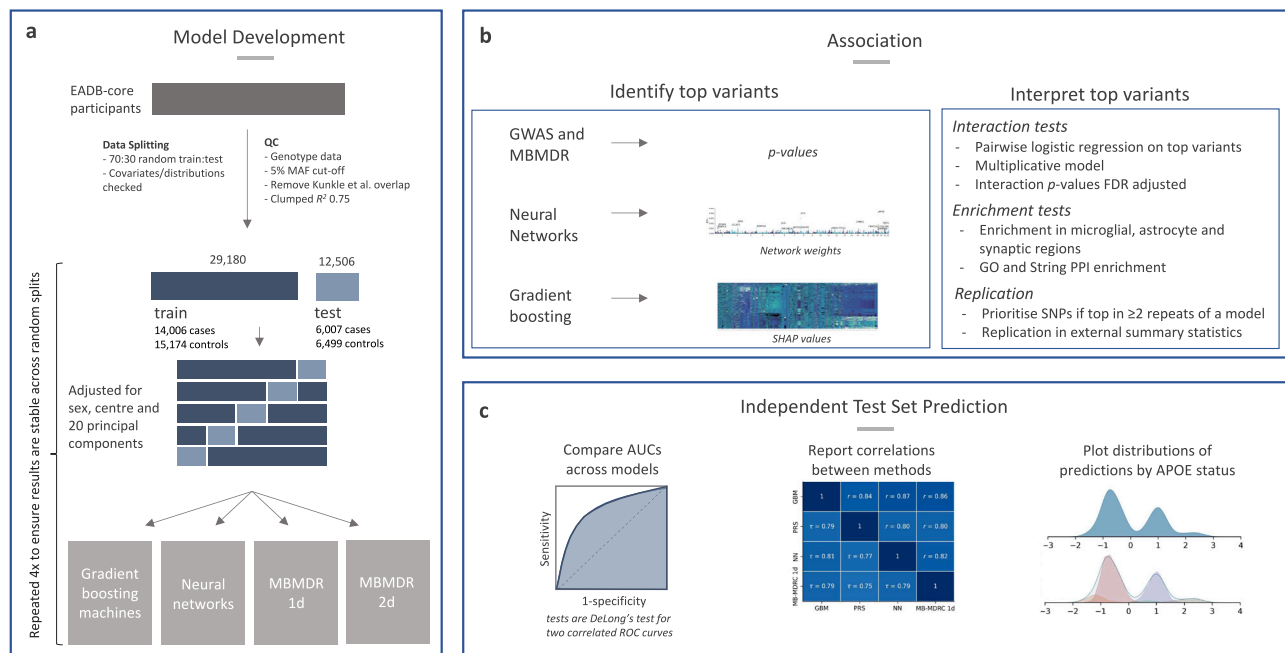


Fig. 1 | Methods overview. Data was separated into an initial balanced random split before model selection (cross-validation and hyperparameter tuning) in the training split (a). All models were subsequently evaluated for association (annotation, enrichment analysis, interaction testing and replication; b) and prediction (AUC and correlations; c). Interaction tests report p-values from the Wald test in logistic

regression (two-sided) as standard, after correction for multiple testing. The full pipeline was run four times per model to assess robustness. For prediction, AUC values, statistical tests, and correlation analyses are based on the initial train-test split. For association, variants were prioritised if they appeared in the top SNP selection in at least two repeats.

novel AD-associated risk loci which were not identified by traditional GWAS.

Results

Prediction

Gradient boosting, neural networks, MB-MDR 1d, and PRS models were compared for discovery and prediction (Fig. 1). Prediction of AD status between models was highly correlated in the test set, having pairwise correlations between $r = 0.80$ and $r = 0.87$ (Fig. 2). The highest correlations were observed for GBM-NN ($r = 0.87$) and GBM-MB-MDR 1d ($r = 0.86$). The weakest correlations were between NNs and PRS ($r = 0.80$). PRS was most strongly correlated with GBMs ($r = 0.84$). For discrimination between cases and controls, the highest AUC of 0.692 (95% CI: 0.683–0.701) was obtained with gradient boosting, and was not significantly different to an AUC of 0.689 (0.679–0.698) for PRS (Fig. 2, Supplementary Data 4). The AUCs remained within the 95% CI when we excluded any imputed variants from the data, indicating no risk of bias from their inclusion (GBMs: 0.683, NN: 0.674, and MBMDR-1d: 0.667 without imputed variants). Predictions remained stable across repeats with different random train-test splits (Supplementary Data 4) and across the cohorts in the data (Supplementary Fig. 6). All models have a greater proportion of females in those predicted to be a case, reflecting the underlying sex differences in the data (59% female, 62% female in cases, 57% in controls), except for GBMs which have a similar proportion in both cases and controls (Fig. 2i).

Identification of AD-associated loci

SNPs prioritized by ML approaches were required to appear in at least two random train-test splits, ensuring more robust associations; they include both known (Table 1) and novel variants (Table 2). Gradient boosting machines correctly distinguished the *APOE* haplotypes (Fig. 3a, showing distinct clusters). Figure 3b further highlights modelling of the *APOE* region across methods, wherein GBMs and NNs correctly identify causal SNPs. Known loci including *CRI*, *BIN1*, *IDUA*, *OTULIN*, *RASAI*, *RASGEFIC*, *CLU*, *ABCA1*, *MS4A**, *PICALM*, *ABCA7*, *APOE*,

and *CASS4* (Table 1) are highlighted by ML models (Fig. 3c). In addition, several novel loci were identified with putative biological evidence for association with AD (*ARHGAP25*, *COG7*, *LINC00924/LOC105369212*, *LY6H*, *SOD1* and *ZNF597*) which were replicated in Jansen et al.²² (Table 2). Association of an exonic missense variant was also highlighted in *AP4E1*, within 500 kb of the known *SPPL2A* locus (Table 2). Neural networks (NN) detected known loci in *APOE*, *BIN1*, *CYP27C1*, *ABCA1* and *ABCA7* (Fig. 3c) and an additional novel locus (*SOD1*), which also replicated in Jansen et al.²² (Table 2). MB-MDR 1d identified SNPs in 24 genes, the majority of which map to the *APOE* region, for at least two train-test splits. Of these, 20 were identified by every possible split, indicating highly stable results. MB-MDR 1d identified SNP-SNP pairs in the *APOE* region gene consistently through every train-test split. Single train-test splits also find genes outside of Chromosome 19 (Supplementary Fig. 7). The majority of candidate novel loci were identified by GBMs, which find multiple loci with evidence for association with AD-related traits such as cognition, pTau, AD age-at-onset and neurofibrillary tangles from previous GWAS (see Table 2 and Supplementary Data 5).

Since ML may identify non-linear SNP-SNP interactions, pairwise interaction tests were performed for all top SNPs identified using machine learning models (Tables 1 and 2). Of 17,205 SNP-SNP pairwise interactions, 13 pairs were significant under a standard regression framework (encoded as a multiplicative interaction) after accounting for multiple testing and excluding pairs where both are within the *APOE* region. The two SNP-SNP pairs with the strongest evidence for association were between SNPs rs405509 and rs600550 ($\beta = 0.058$, $p_{FDR} = 6.8 \times 10^{-5}$), and SNPs rs405509 and rs12421663 ($\beta = -0.056$, $p_{FDR} = 1.8 \times 10^{-4}$), both of which involve SNPs in the *APOE* and *MS4A** regions (Supplementary Data 6, Supplementary section 2.5).

Overlap of genes associated with disease risk across methodologies

Known lead variants in *APOE* and *BIN1* were the most important predictors in GBMs and NNs, with the SNPs used to derive *APOE*

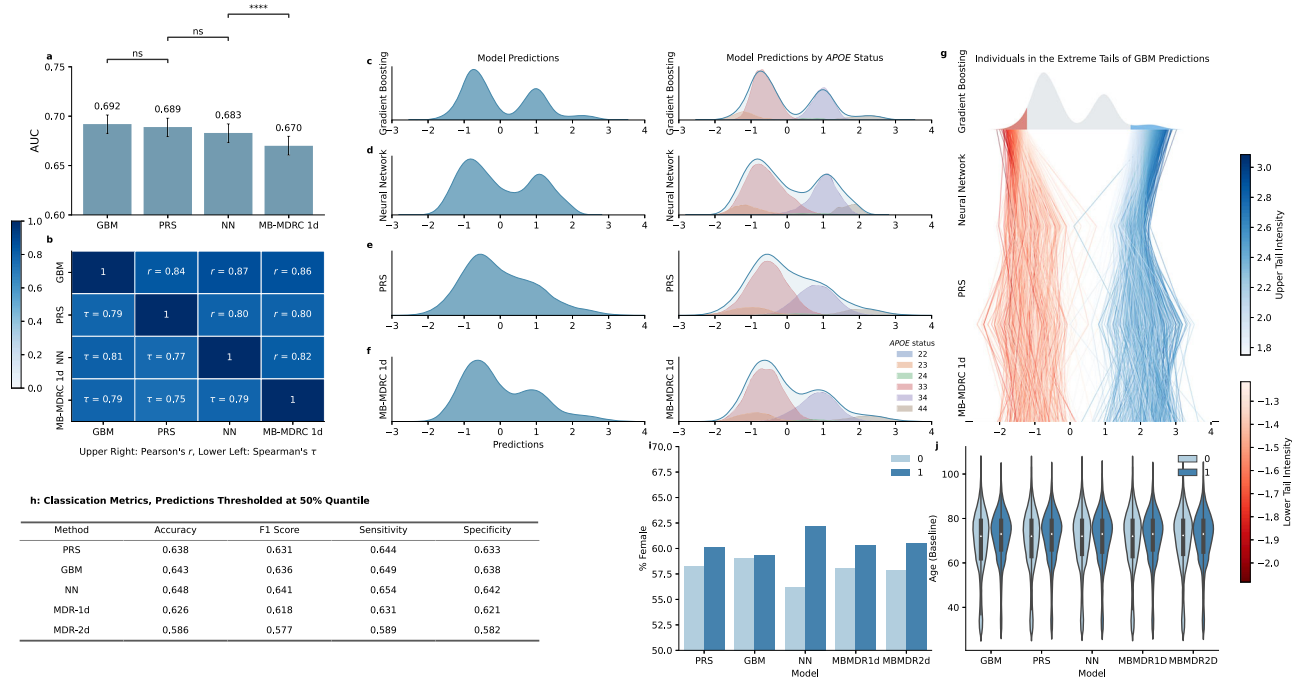


Fig. 2 | Prediction from ML models in the test split for the most predictive models trained with the *APOE* region included. The top two most predictive approaches (GBM, PRS) were not significantly different by AUC, as measured by DeLong's test, though prediction from MB-MDRC 1d was significantly below other methods (a). Bars show the AUC from a single test split for each model, where whiskers are 95% CIs from the pROC package. Unadjusted *p*-values from tests (ns: not significant, ****: *p* < 0.0005) are annotated on panel a for DeLong's two-sided test for correlated ROC curve; see supplementary Data 3 for exact values. Model predictions showed strong correlation, though correlation of the ranks is lower (b). Distributions of covariate-adjusted predictions for the most predictive approaches

are similar but show a more distinct multimodal distribution for GBMs (c), NNs (d) and MB-MDRC 1d (f) compared to PRS (e), illustrating stronger influence of *APOE* risk alleles on predictions. Panel (g) shows the consistency across methods for individuals' prediction scores, where the participants in the 5% extreme tails of GBM predictions are followed across predictions from NN, PRS and MB-MDRC 1d. Classifications metrics are given in (h). Model predictions broken down by covariates are shown in (i) and (j), where dark blue indicates predicted cases, and light blue predicted controls. Box plots in (j) show the median (center line), the 25th and 75th percentiles (box limits), and the whiskers which extend to 1.5 times the interquartile range.

Table 1 | 18 known loci prioritised by machine learning models

Locus	Band	Model	SNP	Gene (Known Locus)
1	1q32.2	A, C	rs6666604,rs1367068*	CR1;CD55
2	2q14.3	A, B, C	rs79527490,rs3754617*	BIN1
3	4p16.3	A, C	rs4690324,rs4690221*	IDUA
4	5p15.2	C	rs31930,rs11133794	OTULIN
5	5q14.3	A, C	rs4141503	RASA1
6	5q35.3	A, C	rs113706587	RASGEF1C
7	6p21.1	C	rs9381040,rs3747742*	TREML2;NFYA
8	6p21.32	A, C	rs3135392,rs6931277*	HLA-DQA2;HLA-DRB5
9	8p21.1	A, C	rs7831810,rs10866859*	EPHX2;CLU;SCARA3 (CLU)
10	8p23.1	C	rs4731,rs1065712	FDFT1
11	9q31.1	B	rs76996768,rs2777800*	ABCA1
12	11q12.2	A, C	rs983392,rs7232*	MS4A6A;MS4A6E
13	11q14.2	A, C	rs536841,rs471470*	PICALM
14	14q32.12	C	rs10498633,rs12590654	RIN3
15	15q21.2	A	rs2306331	AP4E1
16	19p13.3	A, B, C	rs11672916,rs3795065*	ABCA7;CNN2
17	19q13.32	A, B, C, D	rs7412, rs429358*	APOE
18	20q13.31	A, C	rs6069736,rs6127744	RTF2 (CASS4)
19	21q21.3	A	rs2830500,rs2830520	ADAMTS1

Loci are defined as known if genome-wide significant in major AD GWAS (Supplementary Data 1) and containing at least one SNP in the top variant list from an ML model (A: GBM, B: NN, C: MB-MDRC 1d, D: MB-MDRC 2d). Chromosomal bands use build GRCh38p.14 from Ensembl release 111 in BiomaRt. *SNP list curtailed at two rsids: see Supplementary Data 5 for full list.

Table 2 | 34 putative novel loci prioritised from machine learning models

Locus	Band	Model	SNP	Gene	Replication p-value	Summarised GWAS Catalogue Traits
1	2p13.3	A	rs80275456	ARHGAP25	0.0116*	Blood count, Psychiatric disorders, Lipid metabolism
2	3p21.1	A	rs3774423	CACNA1D	0.7828	CVD, Sleep, Cognition, Adiposity, Smoking
3	3p24.1	B	rs2371108,rs9828781	EOMES	0.6256	Inflammation, Arthritis, Blood count
4	3p25.1	A	rs7636739	SH3BP5	0.781	Smoking, Alcohol
5	3p25.2	A	rs7645264	RPL32	0.9424	Adiposity
6	4q21.22	B	rs17005633	HNRNPDL	0.4745	
7	4q27	A	rs75623120	TRPC3	0.2129	Inflammation
8	4q34.3	A	rs1363592,rs2546251	LINC00290	0.4379	AD in APOE-e4, CSF AB1-42 levels, CAA x APOE-e4, Psychiatric disorders
9	6p21.33	A	rs12210887	LSM2	0.933	Psychiatric disorders, Inflammation, Infection
10	6p22.2	A	rs9393777	BTN3A1	0.6977	Diabetes, Psychiatric disorders, Cognition, Adiposity
11	7p15.3	A	rs11770728	CCDC126	0.0832	Liver, Cardiovascular function
12	7p21.2	A	rs10486769,rs16878585	MEOX2	0.0564	CVD, Lipid metabolism, Brain volume,Adiposity
13	8p12	A	rs76461905,rs11780927	RNF122;DUSP26	0.4174	Sleep, BMI, Pulse pressure
14	8p23.2	A	rs11136920	CSMD1;LOC100287015	0.4383	AD, CVD, Inflammation, Sleep, Diabetes, Psychiatric disorders, Smoking, Lipid metabolism
15	8p23.3	A	rs1550948,rs73175035	FBXO25	0.0617	Inflammation, Alcohol, Moyamoya disease
16	8q21.13	A	rs11778492	ZC2HC1A	0.2123	Depression, Inflammation, Weight
17	8q21.13	A	rs11987678	TPD52	0.6003	Inflammation, Diabetes, Sleep
18	8q24.3	A	rs7013750	LY6H	0.0449*	Smoking, Diabetes, Cognition
19	13q14.13	A	rs9567575	SIAH3	0.8082	NFTs, Clusterin levels, Diabetes, Cortical surface area, Cardiovascular function
20	13q33.1	A	rs1333277	DAOA-AS1;LINC01309	0.0992	Smoking, Diabetes, Cognition, CSF TREM-2, PHF-tau, Adiposity
21	14q11.2	A	rs1107390	DAD1;ABHD4	0.991	Inflammation, liver function
22	14q32.33	A	rs7143644	C14orf180;TMEM179;INF2		Inflammation, Psychiatric disorders
23	15q21.1	A	rs498976	SEMA6D	0.9661	Cognition, Psychiatric disorders, Sleep, Longevity, Smoking, Anthropometric traits
24	15q26.2	A	rs117354036,rs4247092	LINC00924;LOC105369212	0.0345*	Cognition in MCI, Inflammation, Smoking, CVD
25	15q26.2	A	rs12911308	MCTP2	0.0788	CSF pTau in AD, CVD, Inflammation, Diabetes, Psychiatric disorders
26	15q26.3	A	rs12901450,rs8035839	TARS3	0.7071	
27	16p12.2	A	rs250583	COG7	0.001*	Cholesterol x fenofibrate
28	16p13.3	A	rs4786422	ZNF597	0.0227*	
29	17p13.1	C	rs11078722	KCNAB3	0.2143	Smoking, Blood pressure
30	18q12.2	A	rs17561693,rs1941955	MIR4318;MIR924HG;CELF4	0.349	Smoking, Obesity, Diabetes, Psychiatric disorders, Sleep
31	18q21.33	A	rs694419,rs17729530	ZCCHC2	0.2432	PHF-Tau, Sleep, Psychiatric disorders, Inflammation, Cognition, Adiposity
32	20q11.22	A	rs910873	ASIP	0.942	AD AAO, Skin cancer, Smoking
33	21q22.11	B	rs4998557,rs4816407*	SOD1	0.0147*	ALS, Globulin-levels

Top predictors from machine learning models within 500 kb of each other were merged using bedtools v2.27.1, or if functionally or positionally annotated with the same gene. We prioritise the 34 loci which have support from more than one split in a machine learning model (A: GBM, B: NN, C: MB-MDRC 1 d, D: MB-MDRC 2 d) or replication in an external dataset (Jansen et al., 2019²³), defined as at least one SNP from the listed rsIDs in that row of the table which is present at $p \leq 0.05$ in publicly available summary statistics. Chromosomal bands were extracted for GRCh38p.14 from Ensembl release 111 using BiomaRt; gene annotation methodology is described in the methods section. The direction of effect is not included here as for ML approaches no single direction is obtained: different subgroups may have varying associations with the outcome for a given SNP. Consequently, direction of effect is not as informative as in standard GWAS replication studies. Traits related to AD and dementia which were annotated from the GWAS catalogue and summarised; a full list of traits from past GWAS and corresponding PubMed IDs is given in Supplementary Data 5. *SNP list curtailed at two rsids: see Supplementary Data 5 for full list. *Nominally significant in the replication. Putative novel loci (emphasised) are discussed in the manuscript.

status (rs7412 and rs429358) identified and ranked as the most important SNPs by both GBMs and NNs but not by a GWAS in the training set (Fig. 3b). To compare the ML findings with GWAS results, we included SNPs not only identified in the training set in our study, but also all SNPs reported as genome-wide significant by larger meta-analyses (Supplementary Data 1) and applied the same gene annotation strategy as for the top variants from ML models (see “functional annotation and enrichment analysis”). In total, 130 genes were annotated, where more than one gene may be annotated

to the same locus, and the same gene may be annotated to several independent loci. These genes correspond to 86 distinct loci reported in previous publications^{23–25}. Of these, 19 loci were implicated by at least one ML methodology (Supplementary Fig. 8). APOE was found by all methods, seven loci (PICALM, IDUA, RASGEFIC, CLU, CRI, RTF2, RASAI) were found by GBMs and MB-MDRC 1d, and two (ABCA7, BIN1) by MB-MDRC 1d, GBMs and NNs. ABCA1 was only detected by NNs, and two (SPPL2A, ADAMTS1) only by GBMs (Table 1).

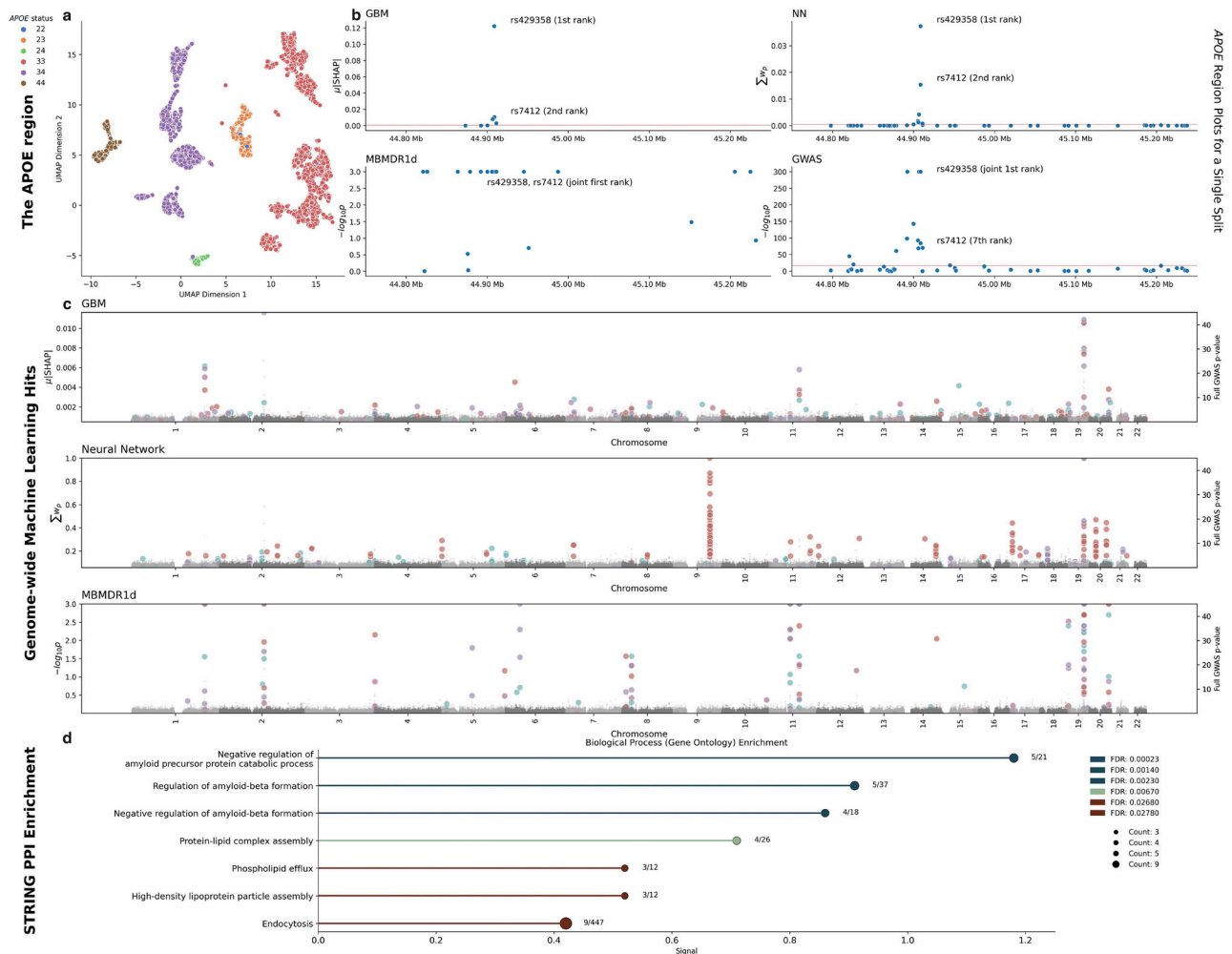


Fig. 3 | Association in ML models. Uniform Manifold Approximation and Projection (UMAP) of raw (unscaled) SHAP values for GBM hits highlights that *APOE* alleles are identified and drive prediction (a). Neural networks and gradient boosting both rank the SNPs required to derive the e2 and e4 allele status for *APOE* as highest, unlike traditional GWAS (b). Values for neural networks and GBMs are not based on p -values, as described below, while p -values in (b,c) (GWAS) are from a logistic regression in the training split, using a logistic regression and p -values from a two-sided Wald test as standard. Manhattan plots are given for top hits only from

gradient boosting (mean absolute SHAP values), neural networks (normalised network layer weights) and MB-MDR 1d ($-\log_{10} p$ -values), where hits from different random splits of the models are shown in different colours, and all variants from a single GWAS on the train split are shown in greyscale for comparison (right hand y-axis) (c). p -values for MB-MDR 1d in (b, c) are derived from a two-sided permutation-based test as implemented in MDMDR^{51,62}. Hits from machine learning models (see Table 2) are enrichment for known Alzheimer's disease processes (d).

Motivated by published evidence suggesting that different variants are associated with the disease depending on *APOE* status, ML models were compared when trained with and without the *APOE* region in the same train-test split. Remarkably, GBMs without the *APOE* region found more known AD risk genes than when trained with *APOE* (see Supplementary section, 2.6), but with lower AUCs (Supplementary Fig. 9).

When the list of SNPs is limited to those which could be identified in the *current data* (using a GWAS in the corresponding training splits), all GWAS-significant SNPs were prioritised by at least one ML approach (Fig. 4). Furthermore, ~84% at the suggestive significance level ($p \leq 10^{-5}$) were retrieved by at least one ML approach.

Enrichment of ML findings in biologically relevant gene sets

The SNPs prioritised by ML (Tables 1 and 2) showed significant enrichment in microglial ($p = 0.0024$) and astrocytic regions ($p = 0.0083$), but not synaptic regions ($p = 0.117$). All 68 genes from 52 loci reported in Tables 1 and 2 were further analysed for protein-protein interaction scores using the online tool STRING (Supplementary

Fig. 10). Pathway analyses demonstrated enrichment in various gene-ontology (GO) pathways (Fig. 3d, Supplementary Data 7). As expected, GO pathways yielded a number of biological processes of interest to Alzheimer's disease, including regulation of amyloid beta formation ($p_{FDR} = 0.0014$) and regulation of amyloid precursor protein catabolic process ($p_{FDR} = 0.00023$, Fig. 3d).

Discussion

In leveraging the largest genotyped case-control AD dataset, this study demonstrates that the current scale of data has reached a threshold where ML can achieve similar predictive accuracy to classical methods and uncover novel genetic insights into AD. Gradient boosting, neural networks, and multifactor dimensionality reduction were selected due to their prominence in the field, demonstrated performance, and complementary strengths. These methods offer distinct advantages: highly performant tree ensembles (GBMs), flexible networks incorporating prior knowledge (NNs), and detection of SNP-SNP interactions (MB-MDR)²⁶. Here they were applied to identify novel genes not detectable via GWAS, and to compare ML prediction accuracies with PRS.

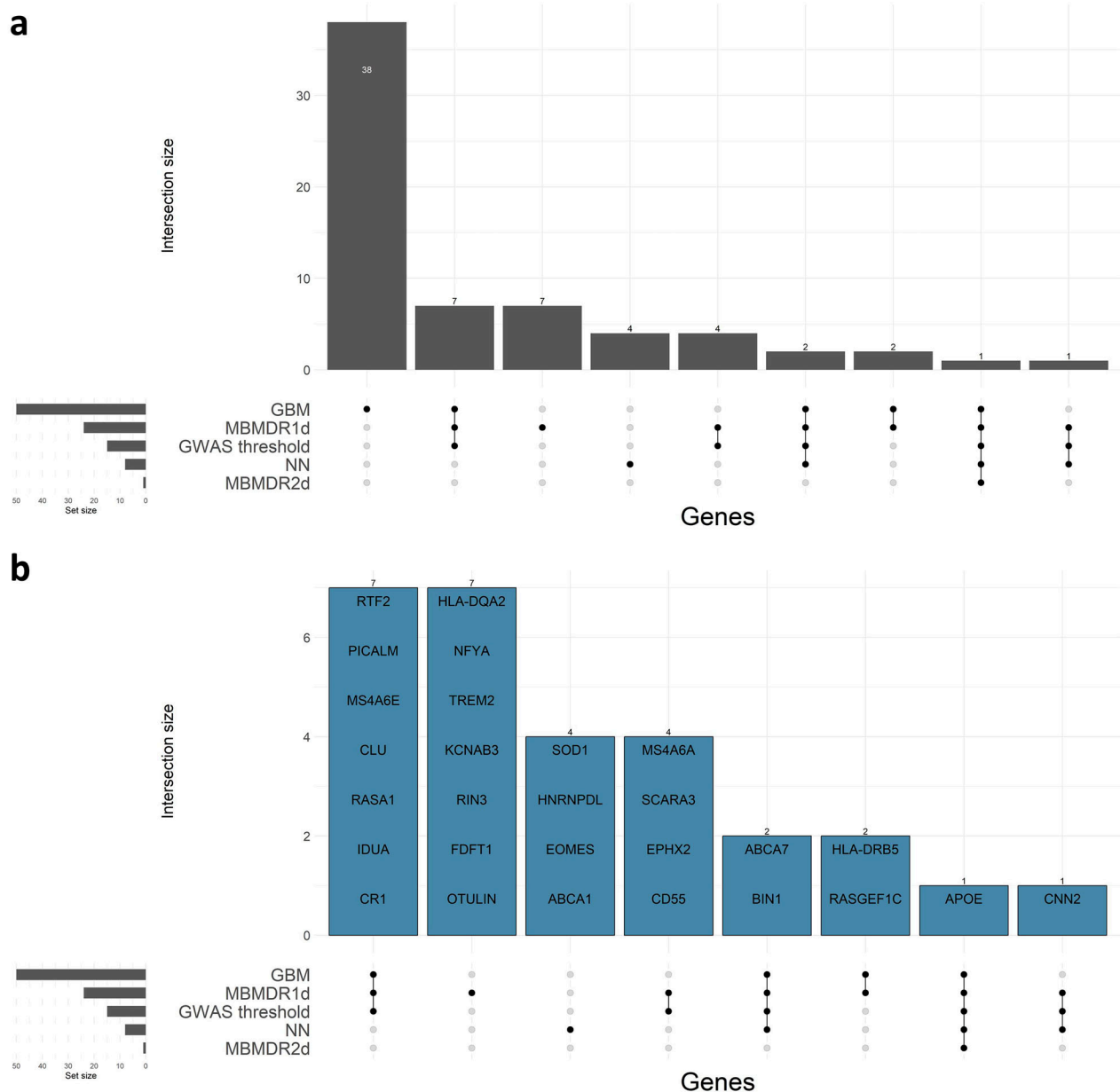


Fig. 4 | UpSet plot showing the overlap between ML and GWAS significant findings from the train part of the train-test split. a Genes mapped by the SNPs highlighted by each ML approach separately. Both ML approaches and GWAS significant SNPs were identified in the same training split. **b** Genes that are shared among at least two train-test splits. All GWAS genome-wide significant ($p \leq 5 \times 10^{-8}$) SNPs in the train split were also identified by ML approaches.

For simplicity, genes within 500 kb of a known locus or with at least one overlapping gene with the region were annotated only by the locus, including *MS4A6A*, *CSTF1*, *EPHX2*, *CNN2*, *TOMM40/NECTIN2/CLPTM1/BCL3/BCAM/APOC1/APOC2/APOC4* and *DGKQ/FAM53A*, which were mapped to *MS4A**, *CASS4*, *CLU*, *ABCA7*, *APOE* and *IDUA* regions, respectively. Subplots were created using ComplexUpset version 1.3.3.

ML methods correctly identified the lead SNPs used to calculate the *APOE* haplotype, rs7412 and rs429358, as having the greatest impact on the model, in contrast to classical univariable linear models (traditional GWAS) which do not distinguish between top variants by p -value, and rank rs7412 lower (Fig. 3c). PRS for AD risk prediction perform best when modelled with two predictors: PRS calculated without the *APOE* region and a separately coded weighting of the *APOE* e2 and e4 alleles²⁷. Here, we demonstrate that ML approaches can accurately identify *APOE* clusters and achieve comparable prediction accuracy without including the derived *APOE* variable as a second predictor. ML approaches further detected the lead SNPs identified in large meta-analyses GWAS for several key genes, including *BIN1* (rs6733839), *PICALM* (rs3851179), *ABCA7* (rs3752246, a coding variant),

CASS4 (rs6069736) and *CRI* (rs4844610). More broadly, ML highlighted SNPs in around 22% of genes identified by larger meta-analysis GWAS^{23–25}, while comparison to a GWAS undertaken on the same (EADB-core) split that was used to train machine learning models, showed that 100% of genome-wide significant SNPs ($p \leq 5 \times 10^{-8}$) were retrieved by ML approaches. This demonstrates that the majority of findings expected under a linear additive GWAS paradigm can be prioritised using flexible machine learning models. Though strides have been made in ML-based prediction of AD from genetic data, for example²⁸, to our knowledge we present the first well-powered, genome-wide ML-based gene discovery study detecting nearly a quarter of known genes found in larger GWAS meta-analyses from the literature which contain around twenty times the sample size, while

also identifying multiple putative regions with credible associations to AD biology, marking an important benchmark for these methods.

Putative novel genes which replicate in an independent GWAS consist of *ARHGAP25*, *COG7*, *LINC00924/LOC105369212*, *LY6H*, *SOD1* and *ZNF597*, which have potential relevance to AD. *ARHGAP25* encodes the Arhgap25 protein which is expressed in macrophages where it affects phagocytosis²⁹ through modulation of the actin cytoskeleton³⁰. Wu et al.³¹ demonstrated that Ly6h is among the proteins competing to bind to $\alpha 7$ subunits of nicotinic acetylcholine receptors (nAChRs), which are expressed throughout the brain and enable fast cholinergic transmission at synapses. These proteins function collectively to maintain the optimal $\alpha 7$ assembly required for neuronal function and viability. This delicate balance is disrupted during Alzheimer's disease due to A β -driven reduction in Ly6h. Notably, an increase in Ly6h in human cerebrospinal fluid correlates with elevated Alzheimer's disease severity³¹.

COG7 (Component of Oligomeric Golgi Complex 7) encodes a protein integral to Golgi apparatus function, which is essential for protein glycosylation and trafficking. Disruptions in Golgi function have been implicated in various neurodegenerative disorders, including Alzheimer's disease. Mutations in *COG7* are associated with Congenital Disorders of Glycosylation (CDG)³², which frequently manifest with neurological impairments. Abnormal glycosylation processes have been implicated in Alzheimer's disease pathology, particularly affecting tau protein processing and amyloid precursor protein (APP) metabolism³³.

ML hits which replicate also include the missense variant rs2306331 (*AP4E1*). This is within the known locus of *SPPL2A* (maximum r^2 0.32, minimum distance 177 kb with rs2306331 and GWAS catalogue hits for *SPPL2A*), but may be an independent signal with the region. The *AP4E1* gene encodes the ϵ subunit of adaptor protein complex-4 (AP-4), which facilitates the transport of amyloid precursor protein (APP) from the trans-Golgi network to endosomes. Disruption of the APP-AP-4 interaction enhances γ -secretase-catalysed cleavage of APP to amyloid- β peptide, suggesting that AP-4 deficiency may constitute a potential risk factor for Alzheimer's disease³⁴.

We also note that ML-derived hits in the known loci *IDUA* and *DGKQ* (rs4690324, linked via sQTLs in GTEx to splicing of *IDUA* in the brain³⁵) are also related to heparan sulfate metabolism³⁶, in addition to multiple brain diseases³⁷, traits³⁸, and lipid metabolism³⁹. Neural networks also highlight a new potential AD-relevant locus. All GO-derived pathways, independent of association to AD, were used in the neural network analysis as hidden layers. This approach highlighted SNPs mapping to *SOD1* (cytogenic band 21q22.11), found in the region of *APP* (21q21.3), with lead SNPs from NNs around 5 Mb away from the closest NN-based hits in *APP*. *SOD1* has been widely investigated for its role in antioxidant defense system, showing impaired expression in AD patients^{40,41}, but is currently primarily implicated in ALS.

In our study, we adopted an MB-MDR approach to detect both SNP main effects and pair-wise SNP-SNP interactions. The method is an improvement over classical pair-wise statistical interaction approaches as it can detect more complex interactions. However, it implements a somewhat conservative strategy for variant discovery, as interaction studies are hampered by several factors that can increase the number of false positives including, but not limited to, LD and interference of major loci, which may contribute to phantom epistasis. To address this limitation, we opted for a model-based (MB) form of MDR, though the results did not highlight novel loci.

Comparing individual scores, ML predictions achieved correlations of 0.8–0.84 with PRS, indicating ML models give predictions which are broadly consistent with well-established approaches. It also shows that identification of novel signals through flexible modelling of complex effects will introduce deviations from the predictions of a simple linear additive model. Disease risk prediction from ML, as assessed by AUC, was higher (but not significantly) than PRS. Similar

results have been reported in psychiatry²¹ and coronary artery disease⁴². This is likely to be due to several reasons. First, SNPs in general are (at best) only correlated with the causal variants, making it particularly difficult to detect nonlinear effects and interactions, which are the main potential advantages of ML over PRS. Second, genetic predictors are weak as compared to some other predictors (e.g. biomarkers⁴³), and the upper bound for AUC in complex trait genetics in practice falls substantially below 1⁴⁴. Weak predictor-response relationships are an inherent challenge to finding patterns with flexible models, and complex models may at-present still be under-powered to achieve a clear improvement in AUC. Third, large GWAS discover and replicate SNPs, which in the resulting summary statistics show small association effect sizes. The effect sizes may however be higher in more homogenous samples. For example, the OR for *APOE* is around 3.4 in samples of mean age 72–73 years⁴⁵ but is reduced in samples over 90 years⁴⁶. In pathologically-confirmed samples, which are also generally older than clinical samples, some of the GWAS-derived SNP effect sizes are higher than reported in clinically-assessed AD GWAS⁴⁷. In more homogenous samples in terms of age, population, and cognitive scores (such as The Alzheimer's Disease Neuroimaging Initiative (ADNI)⁴⁸), the AD PRS AUC are higher than that in clinical samples^{49,50}. Thus, summary statistics from large GWAS meta-analyses enable PRS which predict with moderate AUC in any data set, but which do not achieve high accuracy as effect sizes are averaged across many studies with slightly different features such as recruitment criteria and outcome definitions, and therefore genetic architectures, rather than being specific to a particular one.

A similar situation affects variant discovery from flexible models which can detect interactions: nuanced relationships between predictors are notoriously difficult to replicate⁵¹, a situation further complicated by varying LD between tagged and causal variants. Such SNPs may nonetheless represent important loci which impact disease risk in specific contexts without being consistently associated across enough studies and circumstances to reach genome-wide significance under linear models in meta-analyses. While machine learning models here do not show signs of overfitting, and top SNP rankings by SHAP values are consistent in both the train and test splits, many SNPs identified do not replicate in an external dataset, which is also the case for standard GWAS. In particular, in PRS approaches using different priors (for Bayesian models) or LD pruning parameters (in clumping and thresholding approaches), the resulting set of SNPs and their estimated effects will differ^{27,52}. Similarly, when effects of SNPs are jointly estimated in sparse, high-dimensional ML models, either simultaneously or in a stage-wise manner (as in gradient boosting), different top associations and predictions are expected. Despite these caveats, we show that the novel findings suggest SNPs which are biologically relevant to AD.

This study has a number of limitations. First, our study attempted to run and compare reasonably diverse methods for predicting AD risk, with the advantage of implementing them in a unified dataset. As a result, we found that the PRS and ML prediction showed a similar prediction performance based upon ranking individuals according to their prediction scores. The predictions from ML and PRS, however, were highly correlated, explaining the similarity of the prediction accuracies and reducing the likelihood that an ensemble of the different methods would improve prediction. Second, the methods used for selection of top SNPs in interpreting model results reflect inherent differences in how the ML approaches work, and no standard thresholds exist at the moment for identifying important features across these distinct frameworks. This methodological variability, which is a broader challenge in the field, likely contributes to the incomplete overlap between the top SNPs identified by different ML approaches, making replication in external summary statistics a critical step to ensure robust findings. Third, the influence of *APOE* status on model outcomes is a key component of all models in the study. While *APOE*

SNPs were included as predictors, we did not conduct analyses stratified by *APOE* carrier status, especially $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, or $\epsilon 4/\epsilon 4$ carriers. Future work should explore whether predictive accuracy and associations differ meaningfully across these strata. Finally, although our post-hoc analyses indicate that cohort or genotyping centre effects do not drive associations or predictions, alternative machine learning approaches such as federated learning (FL) may improve modelling where underlying predictor distributions diverge⁵³, while also allowing for models which include data from more cohorts without diminishing privacy. Indeed, within a central learning paradigm, current best practices for data harmonisation involve merging datasets based on shared high-quality SNPs that have undergone rigorous quality control, ensuring high imputation accuracy, reasonably large minor allele frequencies (MAF), and other metrics in each separate study. However, these QC steps alone do not guarantee that differences arising from ancestry, clinical assessment criteria, and genotyping chips or batches used to generate the data are fully accounted for. Applying flexible ML within an FL framework leverages the advantages of client-specific data, which is often more homogeneous as it is typically generated locally, within the same population, using similar clinical assessments and the same genotyping chip. Results from each “client” can then inform analyses for other clients by tuning parameters (e.g., increasing or decreasing neural network weights for variants in specific genomic regions), creating a more flexible and adaptive analysis framework.

In conclusion, this study demonstrates that machine learning can uncover both known and novel genetic loci for AD, providing a powerful complement to traditional GWAS while still achieving competitive predictive performance. Though replication challenges remain, ML successfully prioritised established risk loci and identified biologically relevant novel associations, including variants in *ARHGAP25*, *COG7*, *LY6H*, and *SOD1*. These findings highlight ML’s potential to refine our understanding of AD beyond additive genetic effects and expand the toolkit available for maximising discovery from available data. With expanding datasets and computational advances, ML could further enhance risk prediction and gene discovery, particularly through federated learning and multi-omic integration. This study marks a key step toward leveraging ML for deeper insights into AD genetics.

Methods

Data

Data were obtained from the European Alzheimer & Dementia Biobank (EADB) consortium which combines genetic and clinical data from 16 countries and has been described previously²³. All study protocols were reviewed and approved by the respective institutional review boards overseeing the cohorts (see supplementary information for details). Individuals were genotyped at three centres. Data were accessed after quality control procedures and data harmonisation were applied to give the EADB-core sample. All participants are unrelated individuals of European ancestry, encompassing 20,013 clinically defined AD cases and 21,673 control, after excluding participants present in Kunkle et al.⁴⁵. 59% of the sample is female, split as 62% in cases and 57% in controls, with a median age at baseline of 73 (IQR = 14). Data and splitting procedures are described further in Supplementary section 1.1. Informed consent was obtained in writing from all study participants. For individuals with significant cognitive impairment, consent was secured from a caregiver, legal guardian, or other authorized proxy.

Quality control (QC)

Analyses used directly genotyped (non-imputed) variants to ensure high data quality. To avoid excluding key known AD loci not covered in the genotyped data, we also included 67 imputed variants in previously reported genome-wide significant loci^{23–25} (Supplementary Fig. 1) which were not already present in the genotyped data, converting the imputed dosages to the most probable (probability ≥ 0.9)

genotypes, and applying further quality control as described previously²³. Data were further filtered for a minor allele frequency of 5%, to ensure variants were common enough to reliably observe interactions. SNPs were clumped ($R^2 = 0.75$ following Joiret et al.⁵⁴, window = 1 Mb) using stage 1 summary statistics from Kunkle et al.⁴⁵, after removing individuals common between the summary statistics and the genotyped data. Out of 81 SNPs previously reported as genome-wide significant, 52 survived minor allele frequency (MAF) and clumping procedures (Supplementary Fig. 1; Supplementary Data 1), giving a combined 215,193 SNPs (Supplementary section 1.1). Analyses were also run without inclusion of the previously reported 67 imputed variants to confirm that their inclusion did not artificially inflate performance estimates.

Statistics and reproducibility

No statistical method was used to predetermine sample size, as there are no standardised calculations for machine learning. For consistency, all implemented approaches were evaluated using the same QC and random train-test splits of the data (Fig. 1) which were well balanced for case-control status, age-at-baseline or assessment, sex, genotyping centre, and the distribution of all principal components (Supplementary Fig. 2). Participants were randomly separated into 70–30% train-test splits, with the same split applied to all algorithms, resulting in 29,180 individuals in the training set (14,006 cases; 15,174 controls) and 12,506 for testing (6007 cases; 6499 controls), each with 215,193 predictors after quality control procedures. ML models were built with and without SNPs from the *APOE* region (Chr19:44.4–46.5 Mb). In training ML and PRS models, analyses were adjusted for covariates comprising genetic sex, 20 principal component (PCs), and genotyping centre. The adjustment method was altered to be appropriate for each modelling approach: covariates were included in the final layer for NNs, with predictions and importance scores taken from non-covariate nodes (see Supplementary Fig. 3); for GBMs and MB-MDR, covariates were z-transformed and then regressed-off from the data before modelling. All reported area under the receiver operator characteristic curve (AUC) values are calculated on the predicted probabilities from models (without thresholding) and adjusted again for confounders in the test split. We utilise penalisation and cross-validated random (GBMs) or grid-based (NNs and MB-MDR) hyperparameter search to reduce the likelihood of overfitting. Details for training and covariate adjustment are given in Supplementary sections 1.2–1.4. To ensure robust results, stability was assessed by re-running all models on three additional random 70–30% train-test splits of the data.

Gradient boosting machines (GBMs)

GBMs were trained using version 1.7.6 of the XGBoost package⁵⁵, an efficient implementation of regularised gradient boosting, and the dask package⁵⁶, version 2023.1.1, which allows for distributed training of ML models across multiple nodes in a high-performance computing (HPC) cluster. Hyperparameters for learning rate, tree depth, and column sampling fraction were tuned on a random subsample of the training set using random search (Supplementary section 1.2). Importance of all predictors in GBMs was assessed using SHapley Additive exPlanatory (SHAP) values^{57,58}.

Neural networks (NNs)

NN models were built with GenNet⁵⁹, which uses a biologically-driven configuration in which the connections between the input layer, representing SNPs, and the first hidden layer, representing genes, are defined using knowledge available in annotation databases. NN architectures were built with nine hidden layers, including an initial SNP-to-gene layer annotating all SNPs to the nearest gene using annotations from ANNOVAR⁶⁰, followed by layers defined from the hierarchy of terms from the Gene Ontology consortium (GO terms), where

connections between layers progress from local pathways to more general ones as they move deeper through the network, using all available pathway annotations (Supplementary Fig. 3, Supplementary Data 2). Model hyperparameters for batch size, learning rate (LR) and L_1 (default) penalization were tuned during training (Supplementary section 1.3).

Model based multifactor dimensionality reduction (MB-MDR)

A multi-dimensional reduction strategy was implemented using the MB-MDR methodology^{61,62} with MBMDR 4.4.1 software. An approximation routine was used to accelerate permutation-based significance assessment and multiple testing⁶³, when searching for disease-susceptibility multi-locus genotypes, adjusted for confounders. Single and interacting variants under various pair-wise and higher order epistasis models were combined to create multi-locus risk scores (MB-MDR) and estimate an individual's susceptibility to a trait with the MBMDRClassifier package available in R⁶⁴. SNPs and SNP-SNP interactions were included in the MB-MDR risk score if they passed the permutation-based multiple testing corrected threshold that had the best performance in the train split (Supplementary section 1.4).

Polygenic risk scores (PRS)

PRS were calculated with LDAK-Bolt-Predict from the LDAK package, the most predictive heritability and linkage disequilibrium-informed PRS when individual genotypes are available⁶⁵. LDAK-Bolt-Predict reweights variants using Gaussian priors informed by heritability models, shrinking effect sizes without the need for p -value thresholding⁶⁵. To give the same information to both PRS and all machine learning models, PRS were derived using summary statistics which were generated in the training set by running a genome-wide association study (GWAS), adjusting for the same confounders in PLINK v2.00a3.3LM⁶⁶ (Supplementary section 1.5).

Selection of top predictors

The top SNPs identified by machine learning were selected by the permutation-based p -value threshold defined above for MB-MDR ($p_{adj} < 1$), empirically by taking the extreme tail of the distribution for SHAP values ($\mu|SHAP| > 0.0005$) in gradient boosting (Supplementary Fig. 4), summed weights ($p_{adj} < 0.05$) for neural networks (Supplementary Fig. 5), and by applying the Boruta algorithm⁶⁷ (gradient boosting models only). Only SNPs which were present in top SNPs for at least two train-test random data splits of a given method were prioritised. Details on predictor selection are given in Supplementary sections 1.6 and 2.2-2.4.

Replication of top predictors

The prioritised loci were reported as novel if they were identified with more than one split of a machine learning model, replicated at $p \leq 0.05$ significance level in an external independent dataset (Jansen et al.²²) and had no genome-wide hits from AD summary statistics in the GWAS catalogue. The direction of effect for ML approaches is not available as different subgroups may have varying associations with the outcome for a given SNP, and consequently it is not directly reportable as in standard GWAS.

Functional annotation and enrichment analysis

Publicly available tools were used for further annotation: SNPs were annotated with dbSNP build 156⁶⁸. SNPs were initially positionally mapped to genes using ANNOVAR⁶⁰ version 2020-06-07 and Gencode v40, and then reannotated using functional evidence from the Open Targets Genetics portal where available⁶⁹. Genome coordinates use build GRCh38.p14. Pathway analysis and protein-protein interaction from the consensus annotated genes were determined using STRING v12.0⁷⁰ (Supplementary section 1.7).

The list of top SNPs within each ML analysis was tested for enrichment in the list of genes expressed in microglia ($n = 761$)⁷¹, astrocytes ($n = 757$)⁷², and synapses ($n = 1535$)⁷³, with a window size of 35 kilobase (kb) upstream and 10 kb downstream of regions to include regulatory elements. To account for non-independent SNPs in the genomic regions, enrichment p -values were derived using a bootstrap approach (Supplementary section 1.8) and presented without correction for multiple testing for the number of cell types tested.

Statistical interactions

The ML methods used may include interactions but not explicitly test for them. The top SNPs from all ML approaches (Tables 1 and 2) were therefore formally tested for pair-wise interactions in the whole dataset under a regression framework, assuming a multiplicative relationship between SNPs, i.e. $\text{logit}(y) = \beta_0 + \beta_1 \text{SNP}_1 + \beta_2 \text{SNP}_2 + \beta_3 \text{SNP}_1 * \text{SNP}_2$, where SNPs are coded additively (0, 1, 2) with zero-count compensation, and covariates are included in the model. Pairs were assessed by the p -value for the interaction term after adjusting for multiple comparisons using a false discovery rate (FDR) Benjamini-Hochberg ($p = 0.05$) threshold for significance (Supplementary section 1.9). Putative SNP interactions were visualized in python using shap 0.41⁵⁸, statsmodels 0.13.5⁷⁴, matplotlib 3.7.1⁷⁵, and seaborn 0.12.2⁷⁶. The overall workflow is presented in Fig. 1.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The raw data are protected and are not publically available due to data privacy laws. They can be accessed by application to the EADB consortium. The data generated in this study are provided in the Supplementary Information file.

Code availability

Code for running biologically-informed neural networks via GenNet and Tensorflow is already published and available (<https://github.com/ArnovanHilten/GenNet>). Code used for running distributed gradient boosting using dask and XGBoost (DAXOS v0.1.0) with covariate adjustment, preprocessing of genotypes, and applying distributed Boruta-SHAP feature selection has been made publicly available (<https://github.com/seafloor/daxos>)⁷⁷. Pathway annotation and enrichment tests are also available on GitHub (<https://github.com/seafloor/escott-price-lab-pipelines/tree/main/workflows/pathways>). We use MBMDR version 4.4.1 (<http://bio3.giga.ulg.ac.be/index.php/software/mb-mdr>).

References

- Lambert J. C., Ramirez A., Grenier-Boley B., Bellenguez C. Step by step: towards a better understanding of the genetic architecture of Alzheimer's disease. *Mol. Psychiatry* 1–12 (2023).
- Baker, E. & Escott-Price, V. Polygenic Risk Scores in Alzheimer's Disease: Current Applications and Future Directions. *Front Digit Health* **2**, 556191 (2020).
- Nelson, R. M., Pettersson, M. E. & Carlborg, Ö A century after Fisher: time for a new paradigm in quantitative genetics. *Trends Genet.* **29**, 669–676 (2013).
- Lewis C. M., Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* **12** (2020)
- Visscher P. M., et al. 10 Years of GWAS discovery: biology, function, and translation. *Am. J. Hum. Genet.* **101** (2017).
- Liu, C. C. et al. Cell-autonomous effects of APOE4 in restricting microglial response in brain homeostasis and Alzheimer's disease. *Nat. Immunol.* **24**, 1854–1866 (2023). 24:11. 2023 Oct 19.

7. Yin, Z. et al. APOE4 impairs the microglial response in Alzheimer's disease by inducing TGF β -mediated checkpoints. *Nat. Immunol.* **24**, 1839–1853 (2023).
8. Lin, Y. T. et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron* **98**, 1141–1154.e7 (2018).
9. Emrani, S., Arain, H. A., DeMarshall, C. & Nuriel, T. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. *Alzheimer's Res. Ther.* **12**, 1–19 (2020).
10. Ma, Y. et al. Analysis of whole-exome sequencing data for Alzheimer disease stratified by APOE genotype. *JAMA Neurol.* **76**, 1099–1108 (2019).
11. Bracher-Smith, M. et al. Whole genome analysis in APOE4 homozygotes identifies the DAB1-RELN pathway in Alzheimer's disease pathogenesis. *Neurobiol. Aging* **119**, 67–76 (2022).
12. Jun, G. et al. A novel Alzheimer disease locus located near the gene encoding tau protein. *Mol. Psychiatry* **21**, 108–117 (2016).
13. Park, J. H. et al. Novel Alzheimer's disease risk variants identified based on whole-genome sequencing of APOE ϵ 4 carriers. *Transl. Psychiatry* **11**, 1–12 (2021).
14. Escott-Price, V. & Schmidt, K. M. Pitfalls of predicting age-related traits by polygenic risk scores. *Ann. Hum. Genet.* **87**, 203–209 (2023).
15. Ishioka, Y. L. et al. Effects of the APOE epsilon 4 allele and education on cognitive function in Japanese centenarians. *Age* **38**, 495–503 (2016).
16. Hayden, K. M. et al. Cognitive resilience among APOE ϵ 4 carriers in the oldest old. *Int. J. Geriatr. Psychiatry* **34**, 1833 (2019).
17. Abdellaoui, A., Yengo, L., Verweij, K. J. H. & Visscher, P. M. 15 years of GWAS discovery: realizing the promise. *Am. J. Hum. Genet.* **110**, 179–194 (2023).
18. Rowe T. W., et al. Machine learning for the life-time risk prediction of Alzheimer's disease: a systematic review. *Brain Commun.* **3** (2021).
19. Alatrany, A. S., Hussain, A. J., Mustafina, J. & Al-Jumeily, D. Machine learning approaches and applications in genome wide association study for Alzheimer's disease: a systematic review. *IEEE Access* **10**, 62831–62847 (2022).
20. Christodoulou, E. et al. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J. Clin. Epidemiol.* **110**, 12–22 (2019).
21. Bracher-Smith, M., Crawford, K. & Escott-Price, V. Machine learning for genetic prediction of psychiatric disorders: a systematic review. *Mol. Psychiatry* **26**, 70–79 (2020).
22. Jansen, I. E. et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat. Genet.* **51**, 404–413 (2019).
23. Bellenguez, C. et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat. Genet.* **54**, 412–436 <https://www.nature.com/articles/s41588-022-01024-z54:4> [Internet]. [cited 24 Jan 2023].
24. Andrews, S. J., Fulton-Howard, B. & Goate, A. Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. *Lancet Neurol.* **19**, 326–335 (2020).
25. Wightman, D. P. et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat. Genet.* **53**, 1276–1282 <https://www.nature.com/articles/s41588-021-00921-z53:9> [Internet]. [cited 25 Nov 2021].
26. Van Steen K. Travelling the world of gene–gene interactions. *Brief Bioinform* [Internet]. 2012 Jan 1 [cited 28 Feb 2025];13:1–19. Available from: <https://doi.org/10.1093/bib/bbr012>.
27. Leonenko, G. et al. Identifying individuals with high risk of Alzheimer's disease using polygenic risk scores. *Nat. Commun.* **12**, 1–10 (2021). <https://www.nature.com/articles/s41467-021-24082-z12:1> [Internet]. [cited 6 Sep 2021].
28. Zhou, X. et al. Deep learning-based polygenic risk analysis for Alzheimer's disease prediction. *Commun. Med.* **3**, 1–20 (2023). 3:1. 2023 Apr 6.
29. Schlam, D. et al. Phosphoinositide 3-kinase enables phagocytosis of large particles by terminating actin assembly through Rac/Cdc42 GTPase-activating proteins. *Nature. Nat. Commun.* **6**, 1–12 (2015). <https://www.nature.com/articles/ncomms96236:1> [Internet] [cited 28 Feb 2025].
30. Csépanyi-Kömi, R., Sirokmány, G., Geiszt, M. & Ligeti, E. ARHGAP25, a novel Rac GTPase-activating protein, regulates phagocytosis in human neutrophilic granulocytes. *Blood* [Internet]. **119**, 573–582 (2012). [cited 28 Feb 2025].
31. Wu, M., Liu, C. Z., Barrall, E. A., Rissman, R. A. & Joiner, W. J. Unbalanced regulation of α 7 nAChRs by Ly6h and NACHO contributes to neurotoxicity in Alzheimer's disease. *J. Neurosci.* [Internet]. **41**, 8461 (2021). <https://pmc.ncbi.nlm.nih.gov/articles/PMC8513707/> Oct 13 [cited 28 Feb 2025].
32. Wu, X. et al. Mutation of the COG complex subunit gene COG7 causes a lethal congenital disorder. *Nat. Med.* **10**, 518–523 (2004). <https://www.nature.com/articles/nm104110:5> [Internet]. 2004 Apr 25 [cited 28 Feb 2025].
33. Haukedal H., Freude K. K. Implications of glycosylation in Alzheimer's disease. *Front. Neurosci.* [Internet]. Jan 13 [cited 28 Feb 2025];14. Available from: <https://pubmed.ncbi.nlm.nih.gov/33519371/> (2021).
34. Burgos P. V., et al. Sorting of the Alzheimer's disease amyloid precursor protein mediated by the AP-4 complex. *Dev Cell* [Internet]. 2010 Mar 16 [cited 28 Feb 2025];18:425. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2841041/>.
35. GTEx. rs4690324 in DGKQ linked to IDUA through sQTLs [Internet]. [cited 2024 Apr 18]. Available from: <https://www.gtexportal.org/home/snp/rs4690324>.
36. Fabregat A., et al. Reactome. [cited 16 Apr 2024]. IDUA [lysosomal lumen]. Available from: <https://reactome.org/content/detail/R-HSA-1678661> (2017).
37. Nalls, M. A. et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat. Genet.* **46**, 989–993 (2014). <https://www.nature.com/articles/ng.304346:9> [Internet]. 2014 Sep 1 [cited 28 Feb 2025].
38. Grasby K. L., et al. The genetic architecture of the human cerebral cortex. *Science* [Internet]. Mar 20 [cited 2025 Feb 28];367. Available from: <https://pubmed.ncbi.nlm.nih.gov/32193296/> (2020).
39. Lind L. Genetic determinants of clustering of cardiometabolic risk factors in U.K. biobank. *Metab. Syndr. Relat. Disord.* [Internet]. 2020 [cited 28 Feb 2025];18:121–127. Available from: <https://pubmed.ncbi.nlm.nih.gov/31928498/>.
40. Li, Y., Ma, C. & Wei, Y. Relationship between superoxide dismutase 1 and patients with Alzheimer's disease. *Int. J. Clin. Exp. Pathol.* **10**, 3517–3522 (2017).
41. Spisak, K. et al. rs2070424 of the SOD1 gene is associated with risk of Alzheimer's disease. *Neurol. Neurochir. Pol.* **48**, 342–345 (2014).
42. Gola, D., Erdmann, J., Müller-Myhsok, B., Schunkert, H. & König, I. R. Polygenic risk scores outperform machine learning methods in predicting coronary artery disease status. *Genet Epidemiol.* **44**, 125–138 (2020).
43. Blanco, K. et al. Systematic review: fluid biomarkers and machine learning methods to improve the diagnosis from mild cognitive impairment to Alzheimer's disease. *Alzheimer's Res. Ther.* **15**, 1–16 (2023).
44. Wray, N. R., Yang, J., Goddard, M. E. & Visscher, P. M. The genetic interpretation of area under the roc curve in genomic profiling. *PLoS Genet.* **6**, e1000864 (2010).

45. Kunkle, B. W. et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. *Nat. Genet.* **51**, 414–430 (2019). <https://www.nature.com/articles/s41588-019-0358-251-3> [Internet]. 2019 Feb 28 [cited 26 Jul 2021].
46. Farrer, L. A. et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA* **278**, 1349–1356 (1997).
47. Escott-Price, V., Myers, A. J., Huentelman, M. & Hardy, J. Polygenic risk score analysis of pathologically confirmed Alzheimer's disease. *Ann. Neurol.* **82**, 311 (2017).
48. Weber, C. J. et al. The worldwide Alzheimer's disease neuroimaging initiative: ADNI-3 updates and global perspectives. *Alzheimer's Dement.* **7**, e12226 (2021).
49. Leonenko, G. et al. Genetic risk for alzheimer disease is distinct from genetic risk for amyloid deposition. *Ann. Neurol.* **86**, 427–435 (2019).
50. Bellou, E. et al. Age-dependent effect of APOE and polygenic component on Alzheimer's disease. *Neurobiol. Aging* **93**, 69–77 (2020).
51. Frankel, W. N. & Schork, N. J. Who's afraid of epistasis? *Nat. Genet.* **14**, 371–373 (1996).
52. Ding, Y. et al. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. *Nat. Genet.* **54**, 30–39 (2021). <https://www.nature.com/articles/s41588-021-00961-554:1> [Internet]. 2021 Dec 20 [cited 22 Jan 2024].
53. Zhu, H., Xu, J., Liu, S. & Jin, Y. Federated learning on non-IID data: a survey. *Neurocomputing* **465**, 371–390 (2021).
54. Joiret, M., Mahachie John, J. M., Gusareva, E. S. & Van Steen, K. Confounding of linkage disequilibrium patterns in large scale DNA based gene-gene interaction studies. *BioData Min.* **12**, 1–23 (2019).
55. Chen T., Guestrin C. XGBoost. In: *Proc. 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining - KDD '16*. New York, New York, USA. p. 785–794. (ACM Press, 2016).
56. Rocklin M. Dask: parallel computation with blocked algorithms and task scheduling. In: *Proc. 14th Python in Science Conference* (2015);
57. Lundberg S. M., Allen P. G., Lee S. I. A Unified approach to interpreting model predictions. *Adv Neural Inf Process Syst.* **30** (2017)
58. Lundberg, S. M. et al. From local explanations to global understanding with explainable AI for trees. *Nat. Mach. Intell.* **2**, 56–67 (2020).
59. van Hilten, A. et al. GenNet framework: interpretable deep learning for predicting phenotypes from genetic data. *Commun. Biol.* **4**, 1–9 (2021). 4:1. 2021 Sep 17.
60. Wang, K., Li, M. & Hakonarson, H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res.* **38**, e164–e164 (2010).
61. Cattaert, T. et al. Model-based multifactor dimensionality reduction for detecting epistasis in case–control data in the presence of noise. *Ann. Hum. Genet.* **75**, 78–89 (2011).
62. Mahachie John, J. M., Van Lishout, F. & Van Steen, K. Model-based multifactor dimensionality reduction to detect epistasis for quantitative traits in the presence of error-free and noisy data. *Eur. J. Hum. Genet.* **19**, 696–703 (2011).
63. Lishout F. et al. K Van. gammaMAXT: a fast multiple-testing correction algorithm. *BioData Min.* **8** (2015)
64. Gola, D. & König, I. R. Empowering individual trait prediction using interactions for precision medicine. *BMC Bioinforma.* **22**, 74 (2021).
65. Verhaeghe J., Van Der Donckt J., Ongenaes F., Van Hoecke S. Powershap: a power-full shapley feature selection method. 71–87 (2022).
66. Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
67. Kurs, M. B. & Rudnicki, W. R. Feature selection with the boruta package. *J. Stat. Softw.* **36**, 1–13 (2010).
68. Sherry, S. T. et al. dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res.* **29**, 308–311 (2001).
69. Mountjoy, E. et al. An open approach to systematically prioritize causal variants and genes at all published human GWAS trait-associated loci. *Nat. Genet.* **53**, 1527–1533 (2021). 53:11. 2021 Oct 28.
70. Szklarczyk, D. et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.* **51**, D638–D646 (2023).
71. Gosselin, D. et al. An environment-dependent transcriptional network specifies human microglia identity. *Science* **356**, 1248–1259 (1979). 2017.
72. Endo F., et al. Molecular basis of astrocyte diversity and morphology across the CNS in health and disease. *Science*. 2022;378 (1979)
73. Koopmans, F. et al. SynGO: an evidence-based, expert-curated knowledge base for the synapse. *Neuron* **103**, 217–234.e4 (2019).
74. Seabold S., Perktold J. Statsmodels: econometric and statistical modeling with Python. *SciPy*. 92–96 (2010).
75. Hunter, J. D. Matplotlib. *Comput. Sci. Eng.* **9**, 90–95 (2007).
76. Waskom, M. L. seaborn: statistical data visualization. *J. Open Source Softw.* **6**, 3021 (2021).
77. Bracher-Smith M. Machine learning in Alzheimer's disease genetics (2025).

Acknowledgements

We thank the University of Lille's Intensive Scientific Computing Mesocentre. M.B.S. and V.E.P. are supported by the UK Dementia Research Institute [UK DRI-3206] through UK DRI Ltd, principally funded by the Medical Research Council and by the UK Medical Research Council: MR/T04604X/1, MR/P005748/1. K.V.S. has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreements No 813533 (MLFPM) and No 860895 (TransSYS), and FNRS convention PDR T.0294.24 "Expanded PRS embracing pathways and interactions for increased clinical utility". F.M. (Federico Melograna) was also funded by the Marie Skłodowska-Curie grant agreement 860895 (TransSYS). J.W. (Julie Williams) is supported by Moondance Dementia Research Laboratory. B.M.T. and G.R. (Gennady Roshchupkin) are funded by ZonMw VIDI (#09150171910068) and ZonMw Veni grant (1936320) respectively. N.A. is funded by GSK. RG and AD were supported by the Italian Ministry of Health (Ricerca Corrente).

Author contributions

M.B.S., F.M. (Federico Melograna) and B.U. contributed equally to the study conception and design, analysis and interpretation of data, creation of code for analysis and primary drafting and revision of the manuscript. C.B., B.G.B., D.D., A.J.N., P.H., B.M.T., M.H. (Marc Hulsman), I.D.R., R.C.M., A.R. (Agustin Ruiz), R.F.S., N.A., G.R. (Gennady Roshchupkin) and J.C. contributed to the study design, interpretation of data or substantial revisions. K.V.S., C.V.D. and V.E.P. contributed equally to the study conception, interpretation of data, manuscript drafting and substantial revisions. All remaining authors—S.V.D.L., A.C., F.K., O.P., A.S. (Anja Schneider), M.D., D.R., N.S. (Norbert Scherbaum), J.D., S.R.H., L.H., L.M.P., E.D., T.G., J.W. (Jens Wiltfang), S.H.H., S.M. (Susanne Moebus), T.T., N.S. (Nikolaos Scarmeas), O.D.I., F.M. (Fermin Moreno), J.P.T., M.J.B., P.P., R.S.V., V.A., M.B., P.G.G., R.P., P.M. (Pablo Mir), L.M.R., G.P.R., J.M.G.A., E.R.R., H.S., S.H., A.D.M., S.M. (Shima Mehrabian), L.T. (Latchezar Traykov), J.H., M.V., N.S. (Nicolai Sandau), J.Q.T., Y.A.P., H.H., J.V.S., I.R. (Inez Ramakers), F.V., P.S., C.G., G.P., V.G., J.W. (Julie Williams), P.A., A.B., J.F.D., G.N., C.D., F.P. (Florence Pasquier), O.H., S.D., E.G., J.P., R.G., D.G., B.A., P.M. (Patrizia Mecocci), V.S., L.P., A.S. (Alessio Squassina), L.T. (Lucio Tremolizzo), B.B., M.W., B.N., M.S., D.S., I.R. (Innocenzo Rainero), A.D., F.P. (Fabrizio Piras), C.M., G.R., F.J., P.K., T.M., P.S.J., K.S., M.I., M.H. (Mikko Hiltunen), R.S., W.V.D.F., O.A.A., A.R. (Alfredo Ramirez), and those in the EADB umbrella group (see

Supplementary)—contributed to data acquisition and/or minor revisions.

Competing interests

Outside the submitted work, T.G. received consulting fees from AbbVie, Alector, Anavex, Biogen, BMS; Cogthera, Eli Lilly, Functional Neuromodulation, Grifols, Iqvia, Janssen, Noselab, Novo Nordisk, NuiCare, Orphanzyme, Roche Diagnostics, Roche Pharma, UCB, and Vivoryon; lecture fees from Biogen, Eisai, Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, Schwabe, and Synlab; and has received grants to his institution from Biogen, Eisai, and Roche Diagnostics. N.A. received funding from GSK. All other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-025-61650-z>.

Correspondence and requests for materials should be addressed to Kristel Van Steen, Cornelia van Duijn or Valentina Escott-Price.

Peer review information *Nature Communications* thanks Payam Barnaghi, who co-reviewed with Antigone Fogel, Mike Nalls, and the other,

anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

Reprints and permissions information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2025

Matthew Bracher-Smith^{1,2,268}, Federico Melograna^{3,7,268}, Brittany Ulm^{4,5,268}, Céline Bellenguez⁶, Benjamin Grenier-Boley⁶, Diane Duroux⁷, Alejo J. Nevado⁵, Peter Holmans², Betty M. Tijms^{8,9}, Marc Hulsman^{8,9}, Itziar de Rojas^{10,11}, Rafael Campos-Martin^{12,13}, Sven van der Lee^{8,9}, Atahualpa Castillo², Fahri Küçükali^{14,15}, Oliver Peters^{16,17}, Anja Schneider^{18,19}, Martin Dichgans^{20,21,22}, Dan Rujescu²³, Norbert Scherbaum²⁴, Jürgen Deckert²⁵, Steffi Riedel-Heller²⁶, Lucrezia Hausner²⁷, Laura Molina-Porcel^{28,29}, Emrah Düzel^{30,31}, Timo Grimmer³², Jens Wiltfang^{33,34,35}, Stefanie Heilmann-Heimbach³⁶, Susanne Moebus³⁷, Thomas Teges³⁸, Nikolaos Scarmeas^{39,40}, Oriol Dols-Icardo^{41,42}, Fermin Moreno^{42,43,44}, Jordi Pérez-Tur^{42,45}, María J. Bullido^{42,46,47,48}, Pau Pastor^{49,50}, Raquel Sánchez-Valle⁵¹, Victoria Álvarez^{52,53}, Mercè Boada^{42,54}, Pablo García-González⁵⁵, Raquel Puerta⁵⁵, Pablo Mir^{42,56}, Luis M. Real^{42,62}, Gerard Piñol-Ripoll^{59,60}, Jose María García-Alberca^{42,58,61}, Eloy Rodríguez-Rodríguez^{42,62}, Hilka Soininen⁶³, Sami Heikkinen⁶⁴, Alexandre de Mendonça⁶⁵, Shima Mehrabian⁶⁶, Latchezar Traykov⁶⁷, Jakub Hort⁶⁸, Martin Vyhnaek^{69,70}, Nicolai Sandau⁷¹, Jesper Qvist Thomassen⁷¹, Yolande A. L. Pijnenburg⁸, Henne Holstege^{8,72}, John van Swieten⁷³, Inez Ramakers⁷⁴, Frans Verhey⁷⁴, Philip Scheltens⁸, Caroline Graff⁷⁵, Goran Papenberg⁷⁶, Vilmantas Giedraitis⁷⁷, Julie Williams^{1,2}, Philippe Amouyel⁶, Anne Boland⁷⁸, Jean-François Deleuze⁷⁸, Gael Nicolas⁷⁹, Carole Dufouil^{80,81}, Florence Pasquier⁸², Olivier Hanon⁸³, Stéphanie Debette^{84,85}, Edna Grünblatt^{86,87,88}, Julius Popp^{89,90,91}, Roberta Ghidoni⁹², Daniela Galimberti^{93,94}, Beatrice Arosio^{95,96}, Patrizia Mecocci^{97,98}, Vincenzo Solfrizzi⁹⁹, Lucilla Parnetti¹⁰⁰, Alessio Squassina¹⁰¹, Lucio Tremolizzo¹⁰², Barbara Borroni^{92,103,104}, Michael Wagner^{18,105}, Benedetta Nacmias^{106,107}, Marco Spallazzi¹⁰⁸, Davide Seripa¹⁰⁹, Innocenzo Rainero¹¹⁰, Antonio Daniele^{111,112}, Fabrizio Piras¹¹³, Carlo Masullo¹¹⁴, Giacomina Rossi¹¹⁵, Frank Jessen^{18,116,117}, Patrick Kehoe¹¹⁸, Tsolaki Magda^{38,119}, Pascual Sánchez-Juan^{42,120}, Kristel Sleegers^{14,15}, Martin Ingelsson^{121,122,123}, Mikko Hiltunen⁶⁴, Rebecca Sims², Wiesje van der Flier⁸, Ole A. Andreassen^{124,125}, Agustín Ruiz^{42,126,127}, Alfredo Ramirez^{12,18,105,128,129}, EADB*, Ruth Frikke-Schmidt^{71,130}, Najaf Amin⁴, Gennady Roshchupkin^{131,132}, Jean-Charles Lambert⁶, Kristel Van Steen^{3,7,269} ✉, Cornelia van Duijn^{4,5,133,269} ✉ & Valentina Escott-Price^{1,2,269} ✉

¹School of Medicine, Cardiff University, Cardiff, UK. ²Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neuroscience, School of Medicine, Cardiff University, Cardiff, UK. ³BIO3 - Systems Medicine, Department of Human Genetics, KU Leuven, Leuven, Belgium. ⁴Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. ⁵Centre for Artificial Intelligence in Precision Medicine, University of Oxford, Oxford, United Kingdom. ⁶Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, LabEx DISTALZ - U1167-RID-AGE Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Lille, France. ⁷BIO3 - Systems Genetics, GIGA-R Molecular and Computational Biology, University of Liege, Liege, Belgium. ⁸Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands. ⁹Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije

University, Amsterdam, The Netherlands. ¹⁰Research Center and Memory Clinic, ACE Alzheimer Center Barcelona. Universitat Internacional de Catalunya, Catalunya, Spain. ¹¹Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain. ¹²Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ¹³Estudios en Neurociencias y Sistemas Complejos (ENyS) CONICET-HEC-UNAJ, Buenos Aires, Argentina. ¹⁴Complex Genetics of Alzheimer's Disease Group, VIB Center for Molecular Neurology, VIB, Antwerp, Belgium. ¹⁵Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium. ¹⁶German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany. ¹⁷Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute of Psychiatry and Psychotherapy, Hindenburgdamm 30, 12203 Berlin, Germany. ¹⁸German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. ¹⁹Department of Cognitive Disorders and Old Age Psychiatry, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany. ²⁰Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany. ²¹German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. ²²Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ²³Department of Psychiatry and Psychotherapy, Comprehensive Center for Clinical Neurosciences and Mental Health (C3NMH), Medical University of Vienna, Vienna, Austria. ²⁴Department of Psychiatry and Psychotherapy, LVR-Klinikum Essen, University of Duisburg-Essen, Germany Medical Faculty, Essen, Germany. ²⁵Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Würzburg, Germany. ²⁶Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, 04103 Leipzig, Germany. ²⁷Department of Geriatric Psychiatry, Central Institute for Mental Health Mannheim, Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. ²⁸Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic of Barcelona, Fundació Recerca Clínic Barcelona- Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), and University of Barcelona, Barcelona, Spain. ²⁹Neurological Tissue Bank - Biobank, Hospital Clínic-FRCB-IDIBAPS, Barcelona, Spain. ³⁰German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany. ³¹Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany. ³²Center for Cognitive Disorders, Department of Psychiatry and Psychotherapy, Technical University of Munich, School of Medicine and Health, Klinikum rechts der Isar, Munich, Germany. ³³Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany. ³⁴German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany. ³⁵Medical Science Department, iBiMED, Aveiro, Portugal. ³⁶Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany. ³⁷Institute for Urban Public Health, University Hospital of University Duisburg-Essen, Essen, Germany. ³⁸1st Department of Neurology, Medical school, Aristotle University of Thessaloniki, Thessaloniki, Makedonia, Greece. ³⁹Taub Institute for Research in Alzheimer's Disease and the Aging Brain, The Gertrude H. Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA. ⁴⁰1st Department of Neurology, Aiginition Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece. ⁴¹Sant Pau Memory Unit, Institut de Recerca Sant Pau, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. ⁴²CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute of Health Carlos III, Madrid, Spain. ⁴³Department of Neurology. Hospital Universitario Donostia, San Sebastian, Spain. ⁴⁴Neurosciences Area, Instituto Biogipuzkoa, San Sebastian, Spain. ⁴⁵Unitat de Genètica Molecular, Institut de Biomedicina de València-CSIC, Valencia, Spain. ⁴⁶Centro de Biología Molecular Severo Ochoa (UAM-CSIC), Madrid, Spain. ⁴⁷Instituto de Investigación Sanitaria 'Hospital la Paz' (IdIPaz), Madrid, Spain. ⁴⁸Universidad Autónoma de Madrid, Madrid, Spain. ⁴⁹Fundació Docència i Recerca MútuaTerrassa, Terrassa, Barcelona, Spain. ⁵⁰Memory Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain. ⁵¹Alzheimer's disease and other cognitive disorders unit. Service of Neurology. Hospital Clínic of Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain. ⁵²Laboratorio de Genética. Hospital Universitario Central de Asturias, Oviedo, Spain. ⁵³Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Asturias, Spain. ⁵⁴ACE Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain. ⁵⁵Research Center and Memory clinic. ACE Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain. ⁵⁶Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología. Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. ⁵⁷Unidad Clínica de Enfermedades Infecciosas y Microbiología. Hospital Universitario de Valme, Sevilla, Spain. ⁵⁸Departamento de Especialidades Quirúrgicas, Bioquímica e Inmunología. Facultad de Medicina. Universidad de Málaga, Málaga, Spain. ⁵⁹Unitat Trastorns Cognitius, Hospital Universitari Santa Maria de Lleida, Lleida, Spain. ⁶⁰Institut de Recerca Biomedica de Lleida (IRBLleida), Lleida, Spain. ⁶¹Alzheimer Research Center & Memory Clinic, Andalusian Institute for Neuroscience, Málaga, Spain. ⁶²Neurology Service, Marqués de Valdecilla University Hospital (University of Cantabria and IDIVAL), Santander, Spain. ⁶³Institute of Clinical Medicine - Neurology, University of Eastern Finland, Kuopio, Finland. ⁶⁴Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland. ⁶⁵Faculty of Medicine, University of Lisbon, Lisbon, Portugal. ⁶⁶Clinic of Neurology, UH "Alexandrovska", Medical University - Sofia, Sofia, Bulgaria. ⁶⁷Department of Neurology, Medical University - Sofia, Sofia, Bulgaria. ⁶⁸Memory Clinic, Department of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital, Praha, Czech Republic. ⁶⁹Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Praha, Czech Republic. ⁷⁰International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic. ⁷¹Department of Clinical Biochemistry, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark. ⁷²Department of Clinical Genetics, VU University Medical Centre, Amsterdam, The Netherlands. ⁷³Department of Neurology, ErasmusMC, Rotterdam, Netherlands. ⁷⁴Maastricht University, Department of Psychiatry & Neuropsychologie, Alzheimer Center Limburg, Maastricht, the Netherlands. ⁷⁵Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital-Solna, 171 64 Stockholm, Sweden. ⁷⁶Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden. ⁷⁷Dept.of Public Health and Carins Sciences / Geriatrics, Uppsala University, Uppsala, Sweden. ⁷⁸Université Paris-Saclay, CEA, Centre National de Recherche en Génomique Humaine, 91057 Evry, France. ⁷⁹Univ Rouen Normandie, Normandie Univ, Inserm U1245 and CHU Rouen, Department of Genetics and CNRMAJ, F- 76000 Rouen, France. ⁸⁰Inserm, Bordeaux Population Health Research Center, UMR 1219, Univ. Bordeaux, ISPED, CIC 1401-EC, Univ Bordeaux, Bordeaux, France. ⁸¹CHU de Bordeaux, Pole santé publique, Bordeaux, France. ⁸²Univ Lille Inserm 1171, CHU Clinical and Research Memory Research Centre (CMRR) of Distal Lille France, Lille, France. ⁸³Université de Paris, EA 4468, APHP, Hôpital Broca, Paris, France. ⁸⁴University Bordeaux, Inserm, Bordeaux Population Health Research Center, Bordeaux, France. ⁸⁵Department of Neurology, Bordeaux University Hospital, Bordeaux, France. ⁸⁶Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich, University of Zurich, Zurich, Switzerland. ⁸⁷Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland. ⁸⁸Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland. ⁸⁹CHUV, Old Age Psychiatry, Department of Psychiatry, Lausanne, Switzerland. ⁹⁰Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland. ⁹¹Department of Geriatric Psychiatry, University Hospital of Psychiatry Zürich, Zürich, Switzerland. ⁹²Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ⁹³Neurodegenerative Diseases Unit, Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, IT, Italy. ⁹⁴Dept. of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, IT, Italy. ⁹⁵Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy. ⁹⁶Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy. ⁹⁷Institute of Gerontology and Geriatrics, Department of Medicine and Surgery, University of Perugia, Perugia, Italy. ⁹⁸Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and

Society, Karolinska Institutet, Stockholm, Sweden. ⁹⁹Interdisciplinary Department of Medicine, Geriatric Medicine and Memory Unit, University of Bari “A. Moro”, Bari, Italy. ¹⁰⁰Centre for Memory Disturbances, Lab of Clinical Neurochemistry, Section of Neurology, University of Perugia, Perugia, Italy. ¹⁰¹Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari, Italy. ¹⁰²Neurology Unit, “San Gerardo” hospital, Monza and University of Milano-Bicocca, Milan, Italy. ¹⁰³Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. ¹⁰⁴Cognitive and Behavioural Neurology, Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia, Brescia, Italy. ¹⁰⁵Department of Cognitive Disorders and Old Age Psychiatry, University Hospital Bonn, Medical Faculty, Bonn, Germany. ¹⁰⁶Department of Neuroscience, Psychology, Drug Research and Child Health University of Florence, Florence, Italy. ¹⁰⁷IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy. ¹⁰⁸Department of Medicine and Surgery, Unit of Neurology, University-Hospital of Parma, Parma, Italy. ¹⁰⁹Department of Hematology and Stem Cell Transplant, Vito Fazzi Hospital, Lecce, Italy. ¹¹⁰Department of Neuroscience “Rita Levi Montalcini”, University of Torino, Torino, Italy. ¹¹¹Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy. ¹¹²Neurology Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Rome, Italy. ¹¹³Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy. ¹¹⁴Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy. ¹¹⁵Unit of Neurology V - Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy. ¹¹⁶Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ¹¹⁷Cluster of Excellence Cellular Stress Responses in Aging-associated Diseases (CECAD), University of Cologne, Cologne, Germany. ¹¹⁸Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. ¹¹⁹Laboratory of Genetics, Immunology and Human Pathology, Faculty of Science of Tunis, University of Tunis El Manar, 2092 Tunis, Tunisia. ¹²⁰Alzheimer’s Centre Reina Sofia-CIEN Foundation-ISCIII, 28031 Madrid, Spain. ¹²¹Dept. of Public Health and Caring Sciences / Geriatrics, Uppsala University, Uppsala, Sweden. ¹²²Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada. ¹²³Tanz Centre for Research in Neurodegenerative Diseases, Departments of Medicine and Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario, Canada. ¹²⁴NORMENT Centre, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ¹²⁵Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ¹²⁶Research Center and Memory clinic Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya, Barcelona, Spain. ¹²⁷Biggs Institute for Alzheimer’s and Neurodegenerative Diseases, University of Texas Health Science Center, San Antonio, Texas, USA. ¹²⁸Department of Psychiatry & Glenn Biggs Institute for Alzheimer’s and Neurodegenerative Diseases, San Antonio, TX, USA. ¹²⁹Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Disease (CECAD), University of Cologne, Cologne, Germany. ¹³⁰Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. ¹³¹Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands. ¹³²Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands. ¹³³Department of Epidemiology, ErasmusMC, Rotterdam, The Netherlands. ²⁶⁸These authors contributed equally: Matthew Bracher-Smith, Federico Melograna, Brittany Ulm. ²⁶⁹These authors jointly supervised this work: Kristel Van Steen, Cornelia van Duijn, Valentina Escott-Price. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: kristel.vansteen@uliege.be; cornelia.vanduijn@ndph.ox.ac.uk; EscottPriceV@cardiff.ac.uk

EADB

Iris Jansen^{8,9}, Sven van der Lee^{8,9}, Victor Andrade^{134,135}, Victoria Fernández^{42,126}, Maria-Carolina Dalmaso¹³⁶, Luca Kleineidam^{136,137,138}, Laura Molina-Porcel^{28,29}, Shahzad Ahmad^{133,139}, Dag Aarsland^{140,141}, Amanda Cano^{42,126}, Carla Abdelnour^{42,126}, Emilio Alarcón-Martín^{126,142}, Daniel Alcolea^{41,42}, Montserrat Alegret^{42,126}, Ignacio Alvarez^{50,143}, Nicola J. Armstrong¹⁴⁴, Tsolaki Anthoula^{38,145}, Ildebrando Appollonio^{146,147}, Marina Arcaro¹⁴⁸, Silvana Archetti¹⁴⁹, Alfonso Arias Pastor^{59,60}, Lavinia Athanasiu¹⁵⁰, Henri Bailly⁸³, Nerisa Banaj¹⁵¹, Miquel Baquero¹⁵², Ana Belén Pastor¹⁵³, Roberta Ghidoni⁹², Claudine Berr¹⁵⁴, Céline Besse⁷⁸, Valentina Bessi^{106,155}, Giuliano Binetti¹⁵⁶, Silvia Fostinelli¹⁵⁶, Sonia Bellini⁹², Alessandra Bizarro¹⁵⁷, Rafael Blesa^{41,42}, Mercè Boada^{42,126}, Silvia Boschi¹¹⁰, Paola Bossù¹⁵⁸, Geir Bråthen^{159,160}, Catherine Bresner¹⁶¹, Henry Brodaty^{144,162}, Keeley J. Brookes¹⁶³, Dolores Buiza-Rueda^{42,56}, Katharina Bürger^{164,165}, Vanessa Burholt^{166,167}, Miguel Calero^{42,153,168}, Geneviève Chene^{80,81}, Ángel Carracedo^{169,170}, Roberta Cecchetti⁹⁷, Laura Cervera-Carles^{41,42}, Camille Charbonnier¹⁷¹, Caterina Chillotti¹⁷², Simona Ciccone¹⁷³, Jorgen A. H. R. Claassen¹⁷⁴, Jordi Clarimon^{41,42}, Christopher Clark¹⁷⁵, Elisa Conti¹⁴⁶, Anaïs Corma-Gómez⁵⁷, Antonio Daniele^{111,112}, Guido Maria Giuffrè¹¹¹, Carlo Custodero¹⁷⁶, Delphine Daian⁷⁸, Efthimios Dardiotis¹⁷⁷, Jean-François Dartigues⁸⁴, Peter Paul de Deyn¹⁷⁸, Teodoro del Ser¹⁷⁹, Nicola Denning¹, Janine Diehl-Schmid¹⁸⁰, Mónica Diez-Fairen^{50,143}, Paolo Dionigi Rossi¹⁷³, Srdjan Djurovic¹⁵⁰, Emmanuelle Duron⁸³, Sebastiaan Engelborghs^{181,182,183,184}, Josep Blázquez^{42,126}, Michael Ewers^{164,165}, Tagliavini Fabrizio¹⁸⁵, Sune Fallgaard Nielsen¹⁸⁶, Lucia Farotti¹⁰⁰, Chiara Fenoglio¹⁸⁷, Marta Fernández-Fuertes⁵⁷, Catarina B. Ferreira⁶⁵, Evelyn Ferri¹⁷³, Bertrand Fin⁷⁸, Peter Fischer¹⁸⁸, Tormod Fladby¹²⁵, Klaus Fließbach^{138,189}, Juan Fortea^{41,42}, Tatiana M. Foroud¹⁹⁰, Silvia Fostinelli⁹², Nick C. Fox¹⁹¹, Emlio Franco-Macias¹⁹², Ana Frank-García^{42,47,193}, Lutz Froelich¹⁹⁴, Jose Maria García-Alberca^{42,61}, Pablo García-González¹²⁶, Sebastian Garcia-Madrona¹⁹⁵, Guillermo Garcia-Ribas¹⁹⁵, Ina Giegling¹⁹⁶, Giaccone Giorgio¹⁸⁵, Oliver Goldhardt¹⁸⁰, Antonio González-Pérez¹⁹⁷, Giulia Grande⁷⁶, Emma Green¹⁹⁸, Edna Grünblatt^{86,87,88}, Tamar Guetta-Baranes¹⁹⁹, Annakaisa Haapasalo²⁰⁰, Georgios Hadjigeorgiou²⁰¹, Harald Hampel^{202,203}, John Hardy²⁰⁴, Annette M. Hartmann¹⁹⁶, Ganna Leonenko¹⁶¹, Janet Harwood¹⁶¹, Seppo Helisalmi^{205,206}, Michael T. Heneka^{207,208}, Isabel Hernández^{42,126}, Martin J. Herrmann²⁰⁹, Per Hoffmann³⁶, Clive Holmes²¹⁰, Raquel Huerto Vilas^{59,60}, Marc Hulsman^{8,211}, Geert Jan Biesels²¹², Charlotte Johansson^{213,214}, Lena Kilander⁷⁷, Anne Kinhult Ståhlbom^{213,214}, Miia Kivipelto^{215,216,217,218}, Anne Koivisto^{205,219,220}, Johannes Kornhuber²²¹, Mary H. Kosmidis²²², Carmen Lage^{42,62}, Erika J. Laukka^{76,223}, Alessandra Lauria¹⁵⁷, Jenni Lehtisalo^{205,224}, Ondrej Lerch^{69,70}, Alberto Lleó^{41,42}, Adolfo Lopez de Munain^{42,225}, Seth Love²²⁶, Malin Löwemark⁷⁷, Lauren Luckcuck¹⁶¹, Juan Macías⁵⁷, Catherine A. MacLeod²²⁷, Wolfgang Maier^{135,138}, Francesca Mangialasche²¹⁵, Spallazzi Marco²²⁸, Marta Marquí^{42,126}, Rachel Marshall¹⁶¹, Angel Martín Montes^{42,47,193},

Carmen Martínez Rodríguez²²⁹, Simon Mead²³⁰, Miguel Medina^{42,153}, Alun Meggy¹, Silvia Mendoza⁶¹, Manuel Menéndez-González²²⁹, Pablo Mir^{42,56}, Merel Mol⁷³, Laura Montreal¹²⁶, Kevin Morgan²³¹, Markus M. Nöthen³⁶, Tiia Ngandu²²⁴, Børge G. Nordestgaard^{130,232}, Robert Oloso⁷⁸, Adelina Orellana^{42,126}, Michela Orsini²³³, Maria Capdevila^{42,126}, Alessandro Padovani²³⁴, Caffarra Paolo²³⁵, Marta Martinez-Lucas¹²⁶, Pierre Pericard²³⁶, Juan A. Pineda⁵⁷, Gerard Piñol-Ripoll^{59,60}, Claudia Pisanu²³⁷, Thomas Polak²⁰⁹, Danielle Posthuma⁹, Josef Priller^{16,238}, Raquel Puerta¹²⁶, Olivier Quenez⁷⁹, Inés Quintela¹⁶⁹, Alberto Rábano^{42,153,239}, Luis M. Real^{57,58}, Marcel J. T. Reinders²⁴⁰, Peter Riederer²⁴¹, Claudia Olivé¹²⁶, Eloy Rodriguez-Rodriguez^{42,62}, Arvid Rongve^{242,243}, Irene Rosas Allende^{52,53}, Maitée Rosende-Roca^{42,126}, Jose Luis Royo²⁴⁴, Elisa Rubino²⁴⁵, María Eugenia Sáez¹⁹⁷, Paraskevi Sakka²⁴⁶, Ingvald Saltvedt^{160,247}, Fernando García-Gutiérrez^{42,126}, María Bernal Sánchez-Arjona¹⁹², Florentino Sanchez-Garcia²⁴⁸, Pascual Sánchez-Juan^{42,62}, Raquel Sánchez-Valle²⁴⁹, Sigrid B. Sando^{159,160}, Michela Scamosci⁹⁷, Elio Scarpini^{148,187}, Martin Scherer²⁵⁰, Matthias Schmid^{208,251}, Jonathan M. Schott¹⁹¹, Geir Selbæk^{125,252}, Alexey A. Shadrin¹⁵⁰, Olivia Skrobot²²⁶, Alina Solomon^{205,215}, Sandro Sorbi^{106,107}, Oscar Sotolongo-Grau¹²⁶, Annika Spottke^{208,253}, Eystein Stordal²⁵⁴, Andrea Miguel¹²⁶, Lluís Tàrraga^{42,126}, Niccolò Tesi^{8,211}, Anbupalam Thalamuthu¹⁴⁴, Tegos Thomas³⁸, Latchezar Traykov⁶⁶, Anne Tybjærg-Hansen^{71,130}, Andre Uitterlinden²⁵⁵, Abbe Ullgren²¹³, Ingun Ulstein²⁵², Sergi Valero^{42,126}, Christine Van Broeckhoven^{256,257,258}, Jasper Van Dongen^{14,256,257}, Jeroen van Rooij^{73,259}, Rik Vandenbergh^{260,261}, Jean-Sebastian Vidal⁸³, Maria Gabriella Vita¹¹¹, Jonathan Vogelsgang^{33,262}, Michael Wagner^{189,208}, David Wallon²⁶³, Leonie Weinhold²⁵¹, Gill Windle²²⁷, Bob Woods²²⁷, Mary Yannakoulia²⁶⁴, Miren Zulaica^{42,265}, Mohsen Ghanbari¹³³, Perminder Sachdev^{144,266}, Karen Mather¹⁴⁴ & Mohammad Arfan Ikram²⁶⁷

¹³⁴Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany. ¹³⁵Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany. ¹³⁶Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, 50937 Cologne, Germany. ¹³⁷Department of Cognitive Disorders and Old Age Psychiatry, University of Bonn, Bonn, Germany. ¹³⁸German Center for Neurodegenerative Diseases (DZNE Bonn), Bonn, Germany. ¹³⁹LACDR, Leiden, The Netherlands. ¹⁴⁰Centre of Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway. ¹⁴¹Institute of Psychiatry, Psychology & Neuroscience, PO 70, 16 De Crespigny Park, London SE58AF, UK. ¹⁴²Department of Surgery, Biochemistry and Molecular Biology, School of Medicine, University of Málaga, Málaga, Spain. ¹⁴³Fundació Docència i Recerca MútuaTerrassa and Movement Disorders Unit, Department of Neurology, University Hospital MútuaTerrassa, Terrassa, 08221 Barcelona, Spain. ¹⁴⁴Centre for Healthy Brain Ageing, School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, Australia. ¹⁴⁵Alzheimer Hellas, Thessaloniki, Makedonia, Greece. ¹⁴⁶School of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy. ¹⁴⁷Neurology Unit, "San Gerardo" hospital, Monza, Italy. ¹⁴⁸Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milano, Italy. ¹⁴⁹Department of Laboratory Diagnostics, III Laboratory of Analysis, Brescia Hospital, Brescia, Italy. ¹⁵⁰NORMENT Centre, University of Oslo, Oslo, Norway. ¹⁵¹Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy. ¹⁵²Servei de Neurologia, Hospital Universitari i Politècnic La Fe, Valencia, Spain. ¹⁵³CIEN Foundation/Queen Sofia Foundation Alzheimer Center, Madrid, Spain. ¹⁵⁴Univ. Montpellier, Inserm U1061, Neuropsychiatry: epidemiological and clinical research, PSNREC, Montpellier, France. ¹⁵⁵Azienda Ospedaliero-Universitaria Careggi, Florence, Italy. ¹⁵⁶MAC-Memory Clinic and Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ¹⁵⁷Geriatrics Unit Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy. ¹⁵⁸Experimental Neuro-psychobiology Laboratory, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy. ¹⁵⁹Department of Neurology and Clinical Neurophysiology, University Hospital of Trondheim, Trondheim, Norway. ¹⁶⁰Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway. ¹⁶¹MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neuroscience, School of Medicine, Cardiff University, Cardiff, UK. ¹⁶²Dementia Centre for Research Collaboration, School of Psychiatry, University of New South Wales, Sydney, Australia. ¹⁶³Biosciences, School of Science and Technology, Nottingham Trent University, Nottingham, UK. ¹⁶⁴Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität LMU, Munich, Germany. ¹⁶⁵German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany. ¹⁶⁶Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand. ¹⁶⁷Wales Centre for Ageing & Dementia Research, Swansea University, Wales, New Zealand. ¹⁶⁸UFIEC, Instituto de Salud Carlos III, Madrid, Spain. ¹⁶⁹Grupo de Medicina Xenómica, Centro Nacional de Genotipado (CEGEN-PRB3-ISCIII). Universidade de Santiago de Compostela, Santiago de Compostela, Spain. ¹⁷⁰Fundación Pública Galega de Medicina Xenómica-CIBERER-IDIS, University of Santiago de Compostela, Santiago de Compostela, Spain. ¹⁷¹Univ Rouen Normandie, Normandie Univ, Inserm U1245 and CHU Rouen, Department of Biostatistics and CNRMAJ, F-76000 Rouen, France. ¹⁷²Unit of Clinical Pharmacology, University Hospital of Cagliari, Cagliari, Italy. ¹⁷³Geriatric Unit, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy. ¹⁷⁴Radboudumc Alzheimer Center, Department of Geriatrics, Radboud University Medical Center, Nijmegen, the Netherlands. ¹⁷⁵Institute for Regenerative Medicine, University of Zürich, Schlieren, Switzerland. ¹⁷⁶University of Bari, "A. Moro", Bari, Italy. ¹⁷⁷School of Medicine, University of Thessaly, Larissa, Greece. ¹⁷⁸Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands. ¹⁷⁹Department of Neurology/CIEN Foundation/Queen Sofia Foundation Alzheimer Center, Madrid, Spain. ¹⁸⁰Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Department of Psychiatry and Psychotherapy, Munich, Germany. ¹⁸¹Center for Neurosciences, Vrije Universiteit Brussel (VUB), Brussels, Belgium. ¹⁸²Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. ¹⁸³Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. ¹⁸⁴Department of Neurology, UZ Brussel, Brussels, Belgium. ¹⁸⁵Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy. ¹⁸⁶Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, Denmark. ¹⁸⁷University of Milan, Milan, Italy. ¹⁸⁸Department of Psychiatry, Social Medicine Center East- Donauespital, Vienna, Austria. ¹⁸⁹Department of Neurodegeneration and Geriatric Psychiatry, University of Bonn, 53127 Bonn, Germany. ¹⁹⁰Department of Medical and Molecular Genetics, Indiana University, Indianapolis, Indiana, USA. ¹⁹¹Dementia Research Centre, UCL Queen Square Institute of Neurology, London, United Kingdom. ¹⁹²Unidad de Demencias, Servicio de Neurología y Neurofisiología. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. ¹⁹³Hospital Universitario la Paz, Madrid, Spain. ¹⁹⁴Department of geriatric Psychiatry, Central Institute for Mental Health, Mannheim, University of Heidelberg, Mannheim, Germany. ¹⁹⁵Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain. ¹⁹⁶Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria. ¹⁹⁷CAEBI, Centro Andaluz de Estudios Bioinformáticos, Sevilla, Spain. ¹⁹⁸Institute of Public Health, University of

Cambridge, Cambridge, UK. ¹⁹⁹Human Genetics, School of Life Sciences, Life Sciences Building, University Park, University of Nottingham, Nottingham, UK. ²⁰⁰A.I Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland. ²⁰¹Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus. ²⁰²Sorbonne University, GRC n° 21, Alzheimer Precision Medicine Initiative (APMI), AP-HP, Pitié-Salpêtrière Hospital, Boulevard de l'hôpital, F., 75013 Paris, France. ²⁰³Eisai Inc., Neurology Business Group, 100 Tice Blvd, Woodcliff Lake, NJ 07677, USA. ²⁰⁴Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK. ²⁰⁵Institute of Clinical Medicine - Neurology, University of Eastern, Kuopio, Finland. ²⁰⁶Institute of Clinical Medicine – Internal Medicine, University of Eastern Finland, Kuopio, Finland. ²⁰⁷Department of Neurodegeneration and Geriatric Psychiatry, University of Bonn, Bonn, Germany. ²⁰⁸German Center for Neurodegenerative Diseases (DZNE, Bonn), Bonn, Germany. ²⁰⁹Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital, Wuerzburg, Germany. ²¹⁰Clinical and Experimental Science, Faculty of Medicine, University of Southampton, Southampton, UK. ²¹¹Section Genomics of Neurodegenerative Diseases and Aging, Department of Human Genetics Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands. ²¹²Department of Neurology, UMC Utrecht Brain Center, Utrecht, the Netherlands. ²¹³Karolinska Institutet, Center for Alzheimer Research, Department NVS, Division of Neurogeriatrics, Stockholm, Sweden. ²¹⁴Unit for Hereditary dementias, Karolinska University Hospital-Solna, Stockholm, Sweden. ²¹⁵Division of Clinical Geriatrics, Center for Alzheimer Research, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden. ²¹⁶Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. ²¹⁷Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College London, London, United Kingdom. ²¹⁸Stockholms Sjukhem, Research & Development Unit, Stockholm, Sweden. ²¹⁹Department of Neurology, Kuopio University Hospital, Kuopio, Finland. ²²⁰Department of Neurosciences, University of Helsinki and Department of Geriatrics, Helsinki University Hospital, Helsinki, Finland. ²²¹Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen, and Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany. ²²²Laboratory of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, Greece. ²²³Stockholm Gerontology Research Center, Stockholm, Sweden. ²²⁴Public Health Promotion Unit, Finnish Institute for Health and Welfare, Helsinki, Finland. ²²⁵Department of Neurology, Hospital Universitario Donostia, OSAKIDETZA-Servicio Vasco de Salud, San Sebastian, Spain. ²²⁶Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol BS16 1LE, UK. ²²⁷School of Health Sciences, Bangor University, Bangor, UK. ²²⁸Unit of Neurology, University of Parma and AOU, Parma, Italy. ²²⁹Servicio de Neurología Hospital Universitario Central de Asturias- Oviedo and Instituto de Investigación Biosanitaria del Principado de Asturias, Oviedo, Spain. ²³⁰MRC Prion Unit at UCL, UCL Institute of Prion Diseases, London W1W 7FF, UK. ²³¹Human Genetics, School of Life Sciences, University of Nottingham, NG7 2UH Nottingham, UK. ²³²Department of Clinical Biochemistry, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark. ²³³Department of Neuroscience, Catholic University of Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. ²³⁴Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. ²³⁵DIMEC, University of Parma, Parma, Italy. ²³⁶Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41-UMS 2014-PLBS, bilille, Lille, France. ²³⁷Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy. ²³⁸Department of Neuropsychiatry and Laboratory of Molecular Psychiatry, Charité, Charitéplatz 1, 10117 Berlin, Germany. ²³⁹BT-CIEN, Madrid, Spain. ²⁴⁰Delft Bioinformatics Lab, Delft University of Technology, Delft, The Netherlands. ²⁴¹Center of Mental Health, Clinic and Policlinic of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Wuerzburg, Germany. ²⁴²Department of Research and Innovation, Helse Fonna, Haugesund Hospital, Haugesund, Norway. ²⁴³The University of Bergen, Institute of Clinical Medicine (K1), Bergen, Norway. ²⁴⁴Departamento de Especialidades Quirúrgicas, Bioquímicas e Inmunología, School of Medicine, University of Málaga, Málaga, Spain. ²⁴⁵Department of Neuroscience and Mental Health, AOU Città della Salute e della Scienza di Torino, Torino, Italy. ²⁴⁶Athens Association of Alzheimer's disease and Related Disorders, Athens, Greece. ²⁴⁷Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway. ²⁴⁸Department of Immunology, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain. ²⁴⁹Neurology department-Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain. ²⁵⁰Department of Primary Medical Care, University Medical Centre Hamburg-Eppendorf, 20246 Hamburg, Germany. ²⁵¹Institute of Medical Biometry, Informatics and Epidemiology, University Hospital of Bonn, Bonn, Germany. ²⁵²Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway. ²⁵³Department of Neurology, University of Bonn, Bonn, Germany. ²⁵⁴Department of Psychiatry, Namsos Hospital, Namsos, Norway. ²⁵⁵Department of Internal medicine and Biostatistics, ErasmusMC, Rotterdam, The Netherlands. ²⁵⁶Laboratory of Neurogenetics, Institute Born - Bunge, Antwerp, Belgium. ²⁵⁷Department of Biomedical Sciences, University of Antwerp, Neurodegenerative Brain Diseases Group, Center for Molecular Neurology, VIB, Antwerp, Belgium. ²⁵⁸Neurodegenerative Brain Diseases Group, VIB Center for Molecular Neurology, VIB, Antwerp, Belgium. ²⁵⁹Department of Internal Medicine, ErasmusMC, Rotterdam, The Netherlands. ²⁶⁰Laboratory for Cognitive Neurology, Department of Neurosciences, University of Leuven, Leuven, Belgium. ²⁶¹Neurology Department, University Hospitals Leuven, Leuven, Belgium. ²⁶²Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA, USA. ²⁶³Univ Rouen Normandie, Normandie Univ, Inserm U1245 and CHU Rouen, Department of Neurology and CNRMAJ, F-76000 Rouen, France. ²⁶⁴Department of Nutrition and Dietetics, Harokopio University, Athens, Greece. ²⁶⁵Neurosciences Area. Instituto Biodonostia, San Sebastian, Spain. ²⁶⁶Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia. ²⁶⁷Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.