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Multimodal mediators connecting *APOE4* to dementia

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Abstract

Background: *APOE* $\epsilon 4$ (*APOE4*) is the strongest genetic risk factor for sporadic dementia. Nevertheless, it remains unclear to what extent shared and disease-specific cerebral and peripheral traits mediate *APOE4*-associated dementia risk across major dementia subtypes.

Methods: We integrated multimodal datasets, including neuroimaging (n = 58,876), plasma proteomics (n = 51,623), and plasma metabolomics (n = 267,627), from the UK Biobank to systematically disentangle brain structural and peripheral molecular mediators that connect *APOE4* carriage to incident all-cause dementia (ACD), Alzheimer's disease (AD), and vascular dementia (VaD). We applied multivariable logistic regression for *APOE4* allele dose-response risk estimates, counterfactual causal mediation analysis to identify neural and molecular mediators, and receiver operating characteristic-based predictive modelling stratified by *APOE4* zygosity.

Results: We revealed graded, allele dosage-dependent risk elevations for ACD, AD and VaD among *APOE4* carriers, whereby homozygous carriers exhibited substantially higher incident dementia risk relative to heterozygous carriers and non-carriers across all three clinical endpoints. Bilateral hippocampal and left thalamic gray matter atrophy selectively mediated *APOE4*-associated ACD and AD risk without detectable indirect effects on VaD, while widespread white matter microstructural degeneration mediated increased risk across all three dementia subtypes. At the peripheral molecular level, circulating GFAP served as a shared protein mediator for ACD, AD and VaD, whereas

distinct proteomic and metabolomic profiles underpinned subtype-specific pathways for AD and VaD, respectively. Combined models integrating plasma mediators outperformed clinical-only models for predicting incident dementia in both *APOE4* heterozygotes and homozygotes.

Conclusions: Collectively, this study delineates coordinated central brain structural and circulating molecular mediators of *APOE4*-associated dementia risk, and provides potential subtype-specific mechanistic insights and therapeutic targets for AD and VaD.

Clinical trial number: not applicable.

Keywords: *APOE4*, dementia risk, mediators, white matter, plasma proteomics, predictive models

Background

The apolipoprotein E ϵ 4 (*APOE4*) represents the most robust and well-established genetic risk factor for sporadic Alzheimer's disease (AD) [1, 2], and it also confers elevated susceptibility to Lewy body dementia and vascular dementia (VaD) across aging populations [3, 4]. Carriage of one or two *APOE4* alleles substantially elevates lifetime dementia risk, with earlier symptom onset and accelerated pathological progression observed in both homozygous and heterozygous carriers [1, 2], yet the full biological cascade bridging *APOE4* to clinical dementia occurrence remains incompletely characterized. It has been shown that *APOE4* disturbs pleiotropic

physiological functions spanning cerebral lipid metabolism, glial homeostasis, synaptic integrity, and systemic inflammatory regulation, positioning it as a critical molecular hub connecting cerebral structural integrity and peripheral circulating molecular profiles to dementia risk [1, 5-7]. Although amyloid- β ($A\beta$)-targeted monoclonal antibodies, including lecanemab and donanemab, have represented a landmark advance in AD disease-modifying therapy [8, 9], recent analyses indicate that *APOE4* homozygous carriers derive minimal cognitive benefits from these treatments while exhibiting heightened vulnerability to amyloid-related imaging abnormalities and other adverse events [10, 11]. Therefore, elucidating the underlying intermediate biological pathways that transmit the pathogenic effects of *APOE4* to overt dementia risk carries profound translational value. Such mechanistic insights would facilitate preclinical risk stratification, uncover novel druggable targets, and enable *APOE4*-stratified preventive and therapeutic strategies. Notably, despite substantial progress in *APOE4* research, no unified mechanistic framework has been established to integrate brain structural signatures and peripheral circulating alterations for explaining population-level *APOE4*-linked dementia susceptibility.

Existing independent lines of research have documented multiple layers of intermediate pathways modulated by *APOE4* [1, 5]. Neuroimaging investigations consistently demonstrate that *APOE4* carriage is associated with widespread gray matter atrophy implicated in memory and executive function, including the hippocampus, entorhinal cortex, and temporal lobe [12, 13]. Complementary diffusion

tensor imaging (DTI) work further uncovers that *APOE4* contributes to white matter degeneration, marked by reduced fractional anisotropy (FA) and elevated mean diffusivity (MD) across limbic, commissure and association tracts such as the cingulum, corpus callosum (CC), and inferior fronto-occipital fasciculus (IFOF) [14-17]. Parallel multi-omics analyses have also identified pervasive plasma proteomic and metabolomic perturbations in *APOE4* carriers [6, 18-20], encompassing elevated neuronal injury markers, aberrant lipoprotein profiles, augmented pro-inflammatory mediators, and dysregulated small-molecule metabolites [6, 18-20]. Despite these cumulative observations, several critical conceptual limitations substantially hinder the mechanistic interpretation of *APOE4*-associated dementia pathogenesis. First, no large-scale harmonized population cohorts have comprehensively integrated brain structural alterations and systemic circulating molecular mediators to systematically explain *APOE4*-linked dementia risk. Second, the majority of prior studies confine clinical outcomes exclusively to AD, lacking comparative mediation analyses across all-cause dementia (ACD), AD, and VaD. This critical gap leaves unaddressed the question of whether *APOE4* initiates shared pathogenic cascades or outcome-specific molecular and neural pathways underlying heterogeneous dementia outcomes. Beyond these gaps, no study has yet established *APOE4*-stratified plasma biomarker models for incident dementia risk prediction. Such stratified prognostic modeling is indispensable for precisely identifying high-risk individuals within *APOE4* carrier populations and facilitating targeted preclinical intervention.

Given these critical gaps in mechanistic understanding and the fragmented nature of existing evidence, the present study leverages the deeply phenotyped UK Biobank (UKB) resource to execute a comprehensive multimodal mediation and predictive modeling framework addressing four predefined research objectives. First, we systematically quantify the total associations between *APOE4* carriage and incident ACD, AD, and VaD to characterize genotype-specific risk gradients across heterogeneous dementia outcomes. Second, we implement formal mediation analyses to disentangle the independent mediating effects of gray matter atrophy and white matter microstructural deterioration on the *APOE4*-dementia relationship. Third, parallel mediation models are constructed to evaluate the indirect contributions of the circulating plasma proteome and metabolome, identifying systemic molecules that act as peripheral intermediate mediators linking *APOE4* to subsequent dementia risk. Finally, we construct stratified dementia risk prediction models based on identified plasma mediators separately for *APOE4* heterozygous carriers and homozygous carriers, benchmarking predictive performance to establish genotype-tailored risk screening tools for preclinical aging populations. Collectively, this work will provide a holistic, multi-tiered mechanistic framework for *APOE4*-associated dementia pathogenesis, which could help guide future advances in early-stage disease detection and the development of *APOE4*-stratified targeted therapeutics.

Methods

Study participants

This research has been conducted using the UKB Resource under application number 532248. The UKB cohort is a large prospective population-based study that recruited more than 500,000 participants aged 40–69 years from 22 assessment centers across the United Kingdom between 2006 and 2010 [21]. All participants provided written informed consent, and the UKB core study protocol was approved by the North West Multicenter Research Ethics Committee (reference: 11/NW/0382). All analyses were performed in strict accordance with the principles outlined in the Declaration of Helsinki. We adopted standardized eligibility criteria to screen study participants and integrate multi-modal high-dimensional data for subsequent analyses. Core inclusion criteria included complete baseline demographical records, *APOE* genotype data, accessible International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic data for three dementia endpoints (ACD, AD, and VaD), and valid measurements of at least one modality among cerebral magnetic resonance imaging (MRI), plasma proteome, or plasma metabolome. Stratified by data modality, we included 58,876 participants with high-quality T1-weighted structural MRI and DTI scans for neuroimaging analyses, 51,623 participants with qualified plasma proteomic data covering 2,922 circulating proteins for proteome analyses, and 267,627 participants with valid plasma metabolomic data quantifying 251 small-molecule metabolites for metabolome analyses. Strict multi-level exclusion criteria were shown as below: (1) participants were excluded if they had baseline prevalent dementia subtypes (AD [F00, G30], VaD [F01], secondary dementia [F02], unspecified dementia [F03]), mild neurocognitive disorders, degenerative neurological diseases, or cognitive

impairment-related symptoms (F06.7, G31.8, and R41); (2) individuals with more than 30% missing values across critical confounding covariates (e.g., educational attainment and smoking history) were removed from analyses; (3) we excluded subjects whose neuroimaging scans exhibited severe quality defects, including prominent motion artifacts, incomplete whole-brain coverage, or widespread signal distortion; (4) participants with substandard multi-omics profiling data were discarded, defined as samples harboring extreme signal outliers or featuring over 80% missing molecular features. For eligible participants with partial covariate missingness below the exclusion threshold, multiple imputation by chained equations was performed to impute missing covariate values prior to all statistical analyses. Participants were prospectively followed for a maximum of 18.3 years via national electronic health record linkage, yielding 10,469 incident ACD cases, 4,690 incident AD cases, and 2,335 incident VaD cases for final analytical modeling.

***APOE* genotype**

APOE genotype was ascertained using genome-wide genotyping data from the UKB cohort, relying on two well-established functional single nucleotide polymorphisms (SNPs), rs429358 and rs7412, which jointly determine the canonical *APOE* allelic variants. All enrolled participants were first categorized into six genotype groups based on distinct *APOE* allele combinations, including $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$. For mediation analyses, participants were dichotomized into *APOE4* non-carriers and *APOE4* carriers to enable comprehensive mediator identifications for

APOE4-associated dementia risk across multiple analytical frameworks. To facilitate stratified analyses focusing on the dose-dependent effects of the *APOE4* allele on dementia risk, we further regrouped participants according to $\epsilon 4$ allele dosage into three clinically meaningful subgroups: non-carriers harboring zero $\epsilon 4$ alleles, heterozygous carriers with one $\epsilon 4$ allele, and homozygous carriers carrying two $\epsilon 4$ alleles.

Dementia outcomes

Incident dementia outcomes were ascertained via linkage to UK National Health Service (NHS) electronic health records, integrating four complementary data sources within the UKB: first-occurrence event reports (Field IDs: 131036–131037, 130836–130843), standardized algorithm-defined outcome fields (Field IDs: 42018–42025), national death registry data (Field IDs: 40001, 40002), and hospital inpatient episode summary data (Field IDs: 41270, 41280). Incident AD was defined using ICD-10 codes F00 and G30; incident VaD was defined using codes F01 and G31.0; and incident ACD included all incident dementia cases of any etiology, encompassing the aforementioned AD and VaD diagnoses as well as other dementia subtypes classified by their corresponding ICD-10 codes. To guarantee high accuracy and reliability in subsequent statistical modeling, all incident dementia cases included in the present study were strictly ascertained via official electronic health record linkage rather than relying solely on participant self-report.

Neuroimaging

Structural MRI

All structural brain scans were collected on uniform 3T Siemens Skyra platforms equipped with 32-channel head coils at dedicated UKB imaging hubs. High-resolution sagittal 3D MPRAGE T1-weighted sequences were captured at 1 mm isotropic voxel resolution, with repetition time = 2,000 ms, inversion time = 880 ms, and a scan duration of 4 min 54 s for each participant. All raw T1-weighted volumes were processed through the official centralized UKB neuroimaging pipeline (https://git.fmrib.ox.ac.uk/falmagro/UK_biobank_pipeline_v_1). This standardized workflow incorporated rigid-body motion correction, intensity bias field removal, automated skull stripping, plus affine and nonlinear spatial normalization aligned to the MNI152 standard brain template, followed by tissue segmentation that categorized voxels into gray matter, white matter and cerebrospinal fluid compartments. An automated machine learning-based quality control algorithm was applied to screen all T1 images. Scans with severe motion artifacts, incomplete cranial coverage, severe signal distortion or unsuccessful template registration were discarded. Only participants passing T1 quality control were included, resulting in a final analytical sample of 58,876 individuals. Post-segmentation processing generated total global gray matter, peripheral cortical gray matter, total white matter, and regional gray matter volume measurements derived from FreeSurfer subcortical segmentation and the Destrieux a2009s cortical parcellation atlas. The anatomical regions investigated in this study were shown in Supplementary Table 1. All volumetric measurements were

normalized to whole-brain volume to account for inherent inter-individual differences in cranial anatomy.

Diffusion MRI

Whole-brain multi-shell diffusion MRI scans were acquired consecutively after T1-weighted structural imaging following harmonized acquisition parameters across all UKB dedicated imaging centers. The unified diffusion MRI protocol adopted 2 mm isotropic voxels, a $104 \times 104 \times 72$ matrix, multiband acceleration factor of 3, TR of 3,600 ms, TE of 92 ms, dual b-values (1000 and 2000 s/mm²), 50 distinct diffusion encoding directions for each b-value, and paired reverse phase-encoding blips to facilitate geometric distortion correction. All raw diffusion volumes entered the centralized UKB neuroimaging pipeline (https://git.fmrib.ox.ac.uk/falmagro/UK_biobank_pipeline_v_1) for standardized cohort-wide preprocessing. This workflow incorporated FSL *TOPUP* and *EDDY* tools to sequentially mitigate susceptibility-induced distortions, eddy current biases, and inter-volume head motion, alongside gradient orientation recalibration and non-brain tissue masking guided by co-registered T1 brain templates. Voxel-wise diffusion tensor fitting was implemented to compute two primary microstructural metrics: fractional anisotropy (FA) and mean diffusivity (MD). Tract-averaged FA and MD metrics were extracted for 50 canonical white matter tracts defined by the ICBM-DTI-81 Johns Hopkins University white matter atlas (<https://neuro.debian.net/pkgs/fsl-jhu-dti-whitematter-atlas.html>), such as anterior corona radiata (ACR), subregions of the

corpus callosum (CC), corticospinal tract (CST), hippocampal cingulum (HCg), posterior thalamic radiation (PTR), posterior corona radiata (PCR), inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), internal capsule segments, superior corona radiata (SCR), and uncinate fasciculus (UF).

Plasma proteomics

All plasma specimens included in the present study were acquired from participants during baseline UKB assessment visits conducted between March 2006 and October 2010. Standardized venipuncture procedures were uniformly implemented across all assessment centers, with whole blood collected using K₂-EDTA anticoagulant tubes to stabilize circulating protein components. Following collection, blood samples underwent unified automated centrifugation, plasma isolation, and downstream biobanking processing. Circulating protein profiling was performed by Olink Proteomics using the high-throughput Olink Explore proximity extension assay platform. All raw proteomic data underwent a standardized two-stage quality control and preprocessing pipeline predefined in the official UKB Olink documentation (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/Olink_proteomics_data.pdf). Raw intensity values were log₂-transformed to generate standardized normalized protein expression (NPX) values, ensuring consistent cross-sample and cross-batch comparability. A final set of 2,922 high-quality plasma protein assays was retained for all subsequent statistical analyses, including counterfactual mediation analysis and predictive modelling.

Plasma metabolome

Plasma metabolomic profiling was performed on baseline UKB blood samples also collected March 2006–October 2010, using identical K₂-EDTA venipuncture protocols as plasma proteomics. Untargeted nuclear magnetic resonance (NMR) metabolomics was applied to quantify circulating small molecule metabolites across the study cohort, generating quantitative readouts for a total of 251 distinct metabolite measurements (Supplementary Table 2). These metabolites were categorized into five biologically classes: (1) lipoprotein subfractions, including very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), with corresponding measures of cholesterol (C), free cholesterol (FC), total cholesterol (TC), cholesterol ester (CE), and phospholipids (PL); (2) fatty acids, including saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids; (3) amino acids, including histidine, glutamine, tyrosine, and phenylalanine; (4) small molecular organic acids, including lactate, citrate, acetate, and ketone bodies; (5) glycolysis-related metabolites and other low-molecular-weight metabolites. Raw metabolomic data underwent standardized cohort-wide quality control and preprocessing pipelines established by UKB, including spectral alignment, normalization to internal reference standards, removal of outlier samples with extreme signal deviation, and systematic correction for batch and processing plate technical variation. After complete preprocessing and quality filtering, metabolomic data from 267,627 participants were retained for downstream statistical analyses. Full technical specifications of the NMR

metabolomic platform, sample handling workflows, and data quantification procedures are documented in the official UKB resource (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/NMR_companion_phase2.pdf).

Statistical analysis

All statistical analyses in this study relied on R (version 4.3.1). Baseline participant characteristics spanning demographic, genetic and clinical profiles were tabulated and partitioned according to *APOE4* carriage status captured during long-term follow-up. Continuous phenotypic variables were summarized via mean values $\pm$ standard deviations (SD), while categorical variables were reported as raw counts plus corresponding percentages. The normality of continuous variables was formally assessed via Kolmogorov–Smirnov test. Continuous traits conforming to Gaussian assumptions were intergroup-compared using independent two-sample t-test, while non-normally distributed continuous variables were evaluated with Mann–Whitney U test. Chi-square statistics were deployed to examine group-level differences across all categorical variables. A two-tailed *P*-value threshold of less than 0.05 was defined as the cutoff for statistical significance for all comparative analyses above.

Multivariable logistic regression models were built independently for three dementia outcomes (ACD, AD, VaD). Adjusted covariates included age, sex, educational attainment, ethnic background, Townsend deprivation index (TDI), lifelong smoking history, alcohol consumption history, body mass index (BMI), physical activity levels (metabolic equivalent of task [MET]-h/week), employment status, baseline

diagnoses of common cardiovascular diseases (e.g., hypertension) and metabolic disorders (e.g., type 2 diabetes). Model outputs included odds ratios (ORs) with two-sided 95% confidence intervals (CIs). Bonferroni method was implemented for multiple testing corrections. $P_{adjusted}$ value below 0.05 was designated statistically significant.

Counterfactual mediation analysis was performed using the R mediation package to decompose the total *APOE4* genetic effect on dementia incidence into two causal components. The average causal mediation effect (ACME) quantifies the indirect risk transmitted via each intermediate pathway, whereas the average direct effect (ADE) captures the residual genetic influence independent of the evaluated mediators. Three batches of parallel mediation pipelines ran separately for distinct mediator categories: (1) regional gray matter volumes and tract-specific FA and MD; (2) each circulating plasma protein; (3) individual plasma metabolite. All neuroimaging and metabolic variables were z-score standardized prior to mediation analysis. In contrast, proteomic data quantified as NPX values were incorporated into the models without additional standardization. All intermediate traits underwent two sequential regression screening steps prior to formal causal decomposition. First, linear regression models adjusted for pre-specified covariates estimated coefficients in path a, which quantifies the linear association between *APOE4* carrier status and each mediator, with Bonferroni correction applied to account for the full count of mediators within each data modality. Only mediators showing statistically significant associations in path a post-correction proceeded to next-step screening. Second, binary dementia outcome models were

constructed to derive path b coefficients capturing mediator-dementia relationships adjusted by *APOE4*. These logistic models dynamically switched between standard maximum-likelihood binomial regression and Firth penalized logistic regression (via `brglmFit`) to mitigate biases arising from sparse event counts and complete separation. Path b significance was likewise adjusted via Bonferroni correction within each mediator category. Formal counterfactual mediation decomposition using the mediation R package was exclusively performed on mediators that passed multiple testing thresholds in both path a and path b. For every single candidate mediator across neuroimaging, proteomic and metabolomic datasets, regression coefficients for two sequential paths (*APOE4* genotype → mediator, mediator → dementia diagnosis) were extracted alongside point estimates for ACME and ADE. Bias-corrected 95% CIs were derived through 1,000 rounds of nonparametric bootstrap resampling following official guidance from the mediation package documentation. All *P* values associated with ACME, ADE and individual pathway regression weights received Bonferroni correction calibrated to the total volume of mediators examined within each analytical tier (neuroimaging mediators, proteomic mediators, metabolomic mediators). Only mediators yielding $P_{adjusted} < 0.05$ for ACME were classified as statistically significant intermediate pathways transmitting *APOE4*-associated dementia risk. Independent mediation model sets were fitted for ACD, AD and VaD endpoints to systematically identify outcome-specific cerebral structural traits and peripheral molecular pathways linking *APOE4* carriage to subsequent dementia diagnosis. Gray matter and white matter traits with significant mediating effects were visualized via the `ggseg3d` package

in R.

Logistic regression was used to build dementia risk prediction models incorporating up to five top-ranked significant plasma protein or metabolite mediators. Specifically, we included all significant mediators when fewer than five were identified, to limit model overfitting caused by excessive predictors. Three distinct prediction models were established in the present study: the clinical-only model, which included demographic clinical covariates (age, sex, educational attainment); the mediator-only model, built exclusively on the selected plasma mediators; and the combination model, integrating both clinical covariates and plasma mediators. Receiver operating characteristic (ROC) curve analyses assessed the discriminative performance of these models. The area under curve (AUC) was adopted as the primary quantitative indicator to reflect the model's predictive accuracy, and corresponding 95% CIs were calculated to statistically assess the stability and reliability of the predictive performance. Pairwise comparisons of AUC values across different model types (clinical-only, mediator-only, and combination models) were implemented via the DeLong test to detect statistically significant differences in predictive power between competing models. Only $P_{adjusted} < 0.05$ after Bonferroni correction was designated statistically significant.

Results

Datasets and baseline characteristics

This study was conducted using data from the UKB cohort, which initially included 480,273 participants with comprehensive demographic and clinical data. We

integrated three layers of high-dimensional data for systematic analyses: imaging data measuring cerebral volumetric traits and white matter integrity in 58,876 participants, plasma proteomic data profiling 2,922 proteins in 51,623 participants, plasma metabolomic data quantifying 251 metabolites in 267,627 participants. The schematic depicting the study design, integrated datasets, and sequential analytical workflows is presented in Figure 1. Across the full cohort of 480,273 participants, 136,461 individuals carried the *APOE4* risk allele. This carrier group was stratified into two subgroups, including 125,007 heterozygous carriers and 11,454 homozygous carriers. Table 1 summarizes comprehensive baseline demographic, lifestyle, and clinical characteristics of the full cohort (n = 480,273), stratified by *APOE* genotype status. Rigorous intergroup comparisons revealed multiple significant differences across continuous and categorical variables between *APOE4* carrier and non-carrier subgroups. Specifically, *APOE4* carriers exhibited statistically distinct profiles in age distribution, white ethnic proportion, daily physical activity, and BMI, with consistent genotype-dependent disparities observed in both heterozygous and homozygous subgroups. Further significant differences were detected in alcohol consumption history and the prevalence of major metabolic and cardiovascular disorders across *APOE4* strata. In contrast, no statistically meaningful group differences were identified in sex composition, educational attainment, Townsend deprivation index, employment status, or lifetime smoking history across all genotype subgroups.

Dose-dependent effects of *APOE4* on dementia risk

Figure 2 shows the graded risk associations between *APOE* genotype and three incident dementia outcomes, including ACD, AD, and VaD. Figure 2A presents pooled dementia risk of all *APOE4* carriers relative to non-carriers, revealing significantly elevated odds across all dementia outcomes in *APOE4* carriers. Specifically, *APOE4* carrier status conferred an OR of 3.06 (95% CI = 2.94–3.18) for ACD, 4.44 (95% CI = 4.18–4.71) for AD, and 2.70 (95% CI = 2.49–2.94) for VaD, with all estimates reaching statistical significance. Stratified analyses further delineate clear dose-dependent risk gradients driven by *APOE4* allele dosage, where homozygous carriers consistently exhibited substantially higher dementia odds than heterozygous counterparts for every disease outcome (Figure 2B). For ACD, heterozygotes showed an OR of 2.65 (95% CI = 2.54–2.76), whereas homozygotes carried an amplified risk of 8.36 (95% CI = 7.77–8.99). A comparable dosage pattern emerged for AD, with heterozygote OR reaching 3.72 (95% CI = 3.50–3.97) and homozygote OR surging to 13.81 (95% CI = 12.53–15.20). Although effect magnitudes remained milder for VaD, the dose-response relationship remained robust. Heterozygotes had an OR of 2.38 (95% CI = 2.18–2.59), while homozygotes displayed an OR of 7.01 (95% CI = 6.01–8.14).

The mediating effects of cerebral volumetric traits and white matter traits

Fully adjusted mediation models were implemented to quantify the mediating roles of cerebral structural integrity in pathways linking *APOE4* carriage to dementia risk, with independent models fitted for each dementia outcome (Figure 3). Significant mediating effects were consistently observed for bilateral hippocampal and left thalamic volumes

across both ACD and AD endpoints, showing reduced regional gray matter volume partially mediated elevated dementia risk attributable to *APOE4* carriage (Figure 3A–B and Supplementary Table 3-4). White matter FA-based mediation analyses revealed that altered FA in bilateral HCg and bilateral PTR significantly mediated the associations between *APOE4* and subsequent ACD and AD risk (Figure 3C–D and Supplementary Table 5-6). Moreover, white matter MD-based mediation analyses identified widespread mediating signatures across major projection, association and commissural white matter tracts, including ACR, genu and splenium of CC, SCR, PCR, SLF and tapetum, suggesting pervasive white matter microstructural disruption substantially contributes to *APOE4*-associated pathogenic cascade underlying dementia onset (Figure 3E–F and Supplementary Table 5-6). Supplementary Figure 1 further showed significant mediating effects of core projection and commissural tracts for VaD risk (Supplementary Table 7). Tracts such as left PTR, splenium of CC and left SCR exerted robust indirect effects. Such tract-specific effect divergence highlights distinct mechanistic pathways through which *APOE4* significantly elevates the risk of different dementia endpoints.

The mediating effects of plasma proteins

Fully adjusted mediation models were implemented to characterize plasma protein-mediated pathways linking *APOE4* carriage to incident ACD, AD and VaD (Figure 4 and Supplementary Table 8-10). Significant mediating effects were detected for numerous circulating proteins across all three clinical endpoints, revealing overlapping

and outcome-specific proteomic intermediates spanning glial, neuronal, synaptic and inflammatory signatures. Shared mediating effects of glial fibrillary acidic protein (GFAP) were observed for ACD, AD and VaD, indicating astrocytic reactivity acts as a common intermediate linking *APOE4* to dementia risk (Supplementary Table 8-10). For ACD, robust mediating signals were additionally identified for APOE, VGF nerve growth factor inducible (VGF), cell cycle exit and neuronal differentiation 1 (CEND1), synaptotagmin 1 (SYT1), FURIN and integrin subunit alpha 2 (ITGA2) (Supplementary Table 8). Analyses of AD revealed significant mediation by APOE, VGF, CEND1 and FURIN, recapitulating convergent neuronal and lipoprotein-associated pathways (Supplementary Table 9). In comparison to AD, VaD exhibited a distinct set of mediators including ITGA2, poliovirus receptor (PVR) and spondin 2 (SPON2) alongside GFAP (Supplementary Table 10).

The mediating effects of plasma metabolite measurements

Fully adjusted mediation models were implemented to quantify the mediating effects of circulating metabolites regulating the risk of ACD, AD and VaD (Figure 5 and Supplementary Table 11-13). Distinct sets of lipid mediators emerged across three dementia outcomes, revealing outcome-specific metabolite mediators. For ACD (Figure 5A and Supplementary Table 11), the majority of lipid metabolites, including M-LDL-PL, M-LDL-FC, S-LDL-C, S-LDL-FC, and S-LDL-TL, exerted significant suppressive mediating effects, indicating these metabolites correlate with reduced ACD risk. In contrast, nine metabolites (e.g., Lactate, Leucine, and S-HDL-PL) yielded

positive ACME values and displayed complementary mediating effects, suggesting that these metabolites may promote ACD risk. Mediation analyses restricted to AD identified two selective lipid mediators: Avg Diam of VLDL-Pts and L-LDL-CE%, both yielding negative ACME and suppressive mediating effects on the pathway from *APOE4* to AD risk (Figure 5B and Supplementary Table 12). VaD-specific mediation models revealed an *APOE4*-upregulated LDL-centered lipid mediator panel, including M-LDL-FC, LDL-FC, L-LDL-FC, C-LDL-C, LDL-TL, L-LDL-TL, TC, S-LDL-C, M-LDL-PL, LA, that collectively attenuates VaD risk, yielding uniformly negative ACME values (Figure 5C, Supplementary Table 13).

The predictive plasma signatures for incident dementia in *APOE4* carriers

We developed clinical-only, protein-based, and integrated clinical-protein predictive models and applied ROC analyses with DeLong tests to compare their performance in predicting incident ACD, AD, and VaD across *APOE4* heterozygous and homozygous carrier subgroups (Figure 6). Predictive signatures were built using top outcome-specific protein mediators: five markers for ACD (*APOE*, GFAP, VGF, FURIN, PVR), five for AD (*APOE*, serine protease inhibitor, clade A, member 3 [MENT], GFAP, FURIN, VGF), and four for VaD (GFAP, ITGA2, PVR, SPON2). In both *APOE4* heterozygous and homozygous carriers, combination models exhibited the greatest predictive capacity with statistically superior AUC values relative to clinical-only predictive models (all $P < 0.0001$ for inter-model AUC comparisons in DeLong test). For *APOE4* heterozygotes, the combination models yielded AUCs of 0.872 for ACD, 0.880 for AD,

and 0.910 for VaD. Among *APOE4* homozygotes, corresponding AUCs reached 0.845 for ACD, 0.843 for AD, and 0.898 for VaD. Parallel ROC analyses were further implemented for metabolite-based predictive signatures across the same dementia outcomes (Supplementary Figure 2), with metabolite panels selected from top lipid mediators identified in prior mediation analyses, including M-LDL-PL, M-LDL-FC, S-LDL-C, S-LDL-FC, S-LDL-TL for ACD; Avg Diam of VLDL-Pts and L-LDL-CE% for AD; and M-LDL-FC, LDL-FC, L-LDL-FC, C-LDL-C, M-LDL-PL for VaD. Metabolite-only models demonstrated markedly weak predictive performance, with AUC values ranging from 0.543 to 0.639. The integrated clinical-metabolite models generated marginal numerical improvements in AUC compared with clinical-only models, with combination model AUCs ranging from 0.820 to 0.860; however, most of these subtle elevations didn't reach statistical significance in pairwise DeLong comparisons ($P_{adjusted} < 0.05$ only for inter-model AUC comparisons in ACD risk among *APOE4* heterozygote).

Discussion

This multimodal population cohort delineates shared and subtype-specific cerebral and peripheral molecular mediators bridging *APOE4* carriage to incident ACD, AD and VaD via formal mediation analysis. Consistent with previous observations, *APOE4* was associated with allele dose-dependent elevations in dementia susceptibility, with homozygous carriers presenting substantially higher disease odds than heterozygotes across all three dementia outcomes. Counterfactual mediation analyses identified divergent pathogenic intermediates for different dementia endpoints. Hippocampal and

thalamic gray matter atrophy exclusively mediates ACD and AD risk, whereas widespread white matter microstructural impairment seems to act as a pan-dementia mediator. Although circulating GFAP serves as a universal proteomic mediator across all dementia outcomes, distinct protein and lipid signatures were found to separately regulate *APOE4*-related AD and VaD risk. Our integrated clinical-protein models show promising genotype-stratified predictive performance for dementia risk among *APOE4* carriers. Collectively, these findings help refine mechanistic frameworks underlying *APOE4*-linked dementia pathogenesis and may point toward subtype-specific circulating biomarkers and potential therapeutic targets for AD and VaD.

***APOE4* as a pan-dementia genetic modifier**

Our allele dose-dependent risk analyses substantially extended prior single-outcome AD-focused research by directly comparing graded *APOE4* risk across ACD, AD and VaD within a unified prospective cohort. Consistent with existing AD-centric reports [2], we revealed homozygous *APOE4* carriers display higher AD risk compared to heterozygous carriers and non-carriers, verifying robust effects of $\epsilon 4$ dosage on amyloid- and tau-dependent neurodegeneration [1, 22]. Critically, we resolved a longstanding unresolved discrepancy in previous literature on the association between *APOE4* and VaD risk. Prior small-scale studies yielded conflicting conclusions about whether *APOE4* confers weaker or higher VaD risk [4, 23]. Pendlebury *et al.* (2020) reported that *APOE4* homozygosity confers a higher risk of both pre- and post-stroke dementia [4]. However, a recent study conducted by Zhang *et al.* (2026) reported

controversial results showing that dementia risk is much higher in non-carriers of *APOE4* than carriers [23]. In our large-sample longitudinal study, we demonstrated that *APOE4* is associated with higher VaD risk albeit with relatively smaller effect sizes, implying *APOE4* modulates both neurodegenerative and vascular pathogenic cascades possibly via distinct molecular routes [15, 24-27]. Beyond AD and VaD, recent evidence has shown that *APOE4* is also associated with higher risk of Lewy body dementia and lower age at onset in patients with frontotemporal dementia [28-30]. These findings underscore that *APOE4* is not merely an AD-specific risk gene but a pan-dementia genetic modifier whose pathogenic potency varies according to the primary underlying dementia pathology.

The mediating effects of gray matter and white matter traits

This study performed the first comparative mediation analysis integrating structural and diffusion MRI across three dementia outcomes, overcoming a critical limitation of prior neuroimaging research that largely focused solely on AD within cross-sectional cohorts. Our data identified bilateral hippocampal and left thalamic gray matter atrophy as significant mediators of *APOE4*-related ACD and AD risk, with no detectable indirect effects for VaD risk. This subtype-specific gray matter atrophy pattern in AD-prone individuals aligns with canonical AD pathological signatures dominated by intraneuronal tau deposition and regional neuron loss [31, 32], which are not central to the microvascular ischemic damage defining VaD [33]. By contrast, widespread white matter microstructural disruption acted as a shared mediator across all three dementia

outcomes, corroborating previous findings showing that both AD and VaD exhibit significant white matter degeneration [34-36]. Some earlier small-scale imaging studies detected tract-specific deficits restricted to limbic and commissural pathways among *APOE4* carriers [15, 16, 37]. Our large harmonized dataset extended these observations, confirming *APOE4* induces degeneration not only within limbic and commissural tracts but also across multiple core projection tracts, including bilateral PTR, PCR, ACR and SCR. Collectively, these widespread white matter disruptions constitute a critical intermediate pathway through which *APOE4* elevates overall ACD risk. Further stratified tract-level comparisons uncovered both overlapping and divergent white matter injury signatures distinguishing AD from VaD. Individuals vulnerable to AD displayed far more extensive microstructural deterioration relative to those at risk of VaD, yet the two subtypes shared consistent lesions in the left PTR and splenium of CC. This dichotomy of shared and subtype-unique white matter tract damage demonstrates that *APOE4* may contribute to distinct spatial patterns of white matter breakdown contingent on the divergent genetic and pathological substrates underlying each dementia subtype [38]. Most notably, the universal mediating role of white matter microstructural damage across all dementia endpoints highlights that therapeutic strategies targeting white matter repair may represent a promising, broad-spectrum intervention to mitigate *APOE4*-related dementia risk regardless of clinical dementia subtypes [34].

The mediating effects of plasma proteins

We found GFAP emerged as a universal plasma protein mediator across ACD, AD and VaD, indicating GFAP is a shared molecular mediator linking *APOE4* to neurodegeneration and cerebral small vessel disease [39, 40]. We interpret this common signature as evidence that enhanced astrocytic reactivity represents a convergent pathogenic mechanism for both neurodegeneration and vascular pathology triggered by *APOE4* carriage [41, 42]. Meanwhile, clear subtype-specific proteomic mediator profiles emerged. Lipoprotein and neuronal proteins including APOE, VGF and CEND1 selectively mediated AD risk [1, 43, 44], whereas vascular remodeling proteins ITGA2 and SPON2 may mediate the effects of *APOE4* on VaD risk by regulating vascular functions [45, 46]. Most prior plasma proteome studies focused solely on AD and failed to contrast proteomic mediating pathways against VaD, masking these divergent subtype signatures. Unlike case-control proteomic work vulnerable to reverse causation bias, our prospective mediation design confirms these proteins sit upstream of dementia diagnosis, functioning as intermediate pathogenic transmitters rather than late-stage disease byproducts. This layered proteomic framework establishes distinct peripheral lipid and vascular signaling cascades through which *APOE4* differentially elevates risk for AD versus VaD. We additionally identified a subset of plasma protein mediators that exert specific mediating effects on ACD, with no measurable indirect contributions to pure AD or VaD risk. This finding suggests that these circulating mediators are likely associated with pathological cascades unique to less common dementia subtypes within the broad ACD spectrum. Given the low population prevalence of rare dementias such as frontotemporal

dementia in the UKB cohort, adequately powered studies enriched for these cases will be required to formally validate the mechanistic link between these protein mediators and *APOE4*-related dementia risk.

The mediating effects of plasma metabolites

Our lipid metabolite mediation analyses yielded subtype-resolved lipid signaling insights that have been absent from earlier metabolomic research. We observed a wide panel of circulating lipid metabolites exerting protective effects that offset the elevated dementia risk associated with *APOE4* carriage in the composite ACD group. Distinct subtype-specific LDL-related metabolic signatures emerged when AD and VaD were modeled separately, with negative ACME values persisting across both disease subgroups, suggesting that LDL lipid remodeling can partially counteract *APOE4*-driven neurodegenerative and cerebrovascular pathology. Multiple prior human observational studies have documented measurable shifts in systemic lipid profiles among *APOE4* carriers [47-49], yet few work has contextualized these changes as biologically compensatory mechanisms. Our collective metabolite results support a model where *APOE4* genotype initiates a counter-regulatory shift in peripheral lipid metabolism. This endogenous lipid response acts to curb dementia development rather than amplify disease progression, although such indirect mediating effects only account for less than 5% of the total genetic influence carried by *APOE4*. This observation carries notable novelty relative to the prevailing consensus. Most earlier reports classified elevated LDL-derived metabolites, including LDL-C, as pathological

mediators that accelerate dementia onset [50-52]. Nevertheless, higher cholesterol levels in older individuals have been associated with lower dementia risk [53, 54]. Additionally, a recent longitudinal study has shown that most lipid metabolites exhibited protective effects against dementia occurrence, including LDL-C, LDL-CE, PUFAs, and valine [55]. These epidemiological observations are closely concordant with the protective lipid mediation effects we identified. More specifically, elevated LDL-C correlates with mildly higher dementia risk in statin-treated individuals, whereas a protective association emerges in statin-free participants [56]. Collectively, our mediation results offer mechanistic evidence supporting a partial protective role for LDL-C within the pathogenic cascade of *APOE4*-associated dementia.

Predicting dementia in *APOE4* carriers

We advanced genotype-stratified dementia risk prediction by constructing separate clinical, mediator (protein or metabolite), and combination models for *APOE4* heterozygotes and homozygotes, thereby overcoming a pervasive limitation of existing risk prediction tools that are trained on general populations without accounting for the unique genetic vulnerability of $\epsilon 4$ carriers. This zygosity-specific modeling approach lends tangible clinical utility to individuals with confirmed *APOE4* genotyping, enabling personalized prospective risk assessment tailored to their carrier status. Across all three dementia endpoints, protein-based combination models achieved statistically superior AUC compared to clinical-only models (all $P < 0.0001$, DeLong test), validating the incremental predictive value of subtype-specific plasma proteomic

signatures. By contrast, metabolite-based combination models showed limited incremental predictive value (all $P > 0.05$). Unlike prior predictive studies, which rarely constructed bespoke plasma biomarker panels aligned specifically with the distinct pathological pathways of ACD, AD, and VaD, our analysis exclusively incorporated outcome-specific molecular mediators identified via mediation analyses. This tailored feature selection ensures that our models are better calibrated to capture dementia risk driven by subtype-specific pathological cascades. The resulting stratified ROC curves provide potential, translatable screening workflows that allow clinicians to pinpoint high-risk subgroups among *APOE4* carriers well before overt clinical cognitive decline manifests, thereby establishing a robust foundation for designing preclinical prevention and early intervention strategies that can be fine-tuned according to individual *APOE4* dosage.

Major implications

This work bears both mechanistic and translational implications. Mechanistically, our findings lend support to a tiered pathogenic model whereby *APOE4* may drive dementia pathogenesis by triggering white matter degeneration and astrocytic activation. These shared pathological events represent core intermediate processes that operate across AD and VaD, linking *APOE4* genotype to elevated general dementia risk. Beyond these universal pathological cascades, subtype-selective gray matter atrophy together with plasma proteomic and lipid-metabolic perturbations also contribute to dementia onset in a subtype-dependent manner. Such divergent

molecular and structural alterations could help disentangle the distinct pathogenic pathways underlying AD and VaD among *APOE4* carriers. Clinically, the plasma protein signatures identified in this study hold potential to facilitate minimally invasive predementia risk stratification specifically among *APOE4* carriers. Furthermore, the circulating molecular and white matter mediators identified by this study may offer plausible therapeutic targets, thereby yielding actionable mechanistic insights for future tailored dementia drug development among *APOE4* carriers.

Limitations and future directions

This study contains limitations that merit explicit acknowledgement. Although all peripheral molecular traits were assessed at baseline prior to ascertainment of incident dementia outcomes, we still cannot fully rule out reverse causation scenarios in which baseline molecular changes may reflect early subclinical dementia pathology already present at baseline, rather than representing preceding mediators of subsequent dementia onset. Additionally, our NMR metabolomics platform was limited to quantifying a predefined set of small lipid molecules, leaving untargeted lipid species unmeasured despite their potential to exert meaningful mediating effects on dementia risk. Future research directions include implementing prospective multi-time-point sampling schemes to capture dynamic predementia molecular trajectories and validate the temporal ordering of these mediator events. Complementary large-scale untargeted lipidomic profiling should also be performed to systematically screen additional lipid mediators, which may uncover previously unrecognized molecular

mechanisms differentiating AD- and VaD-related pathological cascades in *APOE4*-carrying individuals.

Conclusions

In summary, this large-scale multimodal prospective study mapped the shared and outcome-specific cerebral and peripheral mediators linking *APOE4* to ACD, AD and VaD. *APOE4* conferred gene dose-dependent elevations in dementia risk, with homozygotes exhibiting far greater odds than heterozygotes across all dementia endpoints. Hippocampal and thalamic gray matter atrophy only mediated ACD and AD risk, while white matter degeneration acted as a pan-dementia mediator. Circulating GFAP represented a universal proteomic mediator, whereas subtype-selective protein and lipid signatures separately regulate *APOE4*-associated AD and VaD risk. Combination models achieved robust genotype-stratified prediction for incident dementia in *APOE4* carriers. Collectively, our findings refine the mechanistic models of *APOE4*-associated dementia pathogenesis and provide translatable subtype-specific biomarkers and therapeutic targets for AD and VaD.

List of abbreviations

ACD: all-cause dementia; ACME: average causal mediation effect; ADE: average direct effect; APOE: apolipoprotein E; AUC: area under the curve; CC: corpus callosum; CIs: confidence intervals; CST: corticospinal tract; DTI: diffusion tensor imaging; FA: fractional anisotropy; GFAP: glial fibrillary acidic protein; HCg: hippocampal cingulum; HDL: high-density lipoprotein; ICD-10: International Statistical Classification of

Diseases and Related Health Problems 10th Revision; IFOF: inferior fronto-occipital fasciculus; LDL: low-density lipoprotein; MD: mean diffusivity; MET: metabolic equivalent of task; MNI: Montreal Neurological Institute; MRI: magnetic resonance imaging; NHS: National Health Service; NMR: nuclear magnetic resonance; NPX: normalized protein expression; OR: odds ratio; PCR: posterior corona radiata; PTR: posterior thalamic radiation; ROC: Receiver Operating Characteristic; SCR: superior corona radiata; SLF: superior longitudinal fasciculus; SNPs: single nucleotide polymorphisms; TDI: Townsend deprivation index; TIV: total intracranial volume; UF: uncinate fasciculus; UKB: UK Biobank; VaD: vascular dementia; VLDL: very-low-density lipoprotein.

Declarations

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Ethics approval statement

Ethical approval for the UKB study was obtained from the North West Multi-Centre

Research Ethics Committee (REC reference: 11/NW/0382). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient consent statement

Written informed consent was obtained from every participant prior to enrollment in the UKB cohort.

Consent for publication

Not applicable.

Data availability statement

The raw data supporting this study were acquired from the UKB database. The analytical codes of this study are available on request from the corresponding author.

Conflict of interest disclosure

The authors declare no competing interests.

Authors' contributions

ZC performed formal analysis, methodology, funding acquisition and wrote the original draft. KY contributed to formal analysis and manuscript review-editing. WT, FL, JL, JN, SZ and YS carried out formal analysis. JDP contributed to manuscript review-editing and data curation. BH was responsible for software programming and visualization. JL and YY provided supervision and funding acquisition for this work. All authors reviewed the manuscript.

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Supplementary information

The online version contains supplementary material available.

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Figure legends

Figure 1. Schematic overview of the study design, multi-omics datasets and sequential analytical pipelines.

Three high-dimensional data layers were integrated: brain structural imaging (white and gray matter metrics, $n = 58,876$), plasma proteome profiling covering 2,922 plasma protein ($n = 51,623$), and plasma metabolome quantification of 251 metabolites ($n = 267,627$). All analyses stratified participants by *APOE4* carrier status (non-carriers vs. heterozygous/homozygous carriers) with three dementia endpoints, including ACD, AD, and VaD. Two independent mediation frameworks quantified intermediate neural and circulating molecular mediators linking *APOE4* genotype to incident dementia, with white matter integrity and gray matter volumetric traits tested as brain-derived mediators and circulating molecules assessed as peripheral mediators. ROC curves further evaluated the predictive performance of plasma mediators for dementia risk among *APOE4* carriers, with AUC calculated for clinical-only, mediator-based, and combination prediction models. Abbreviations: APOE, Apolipoprotein E; ACD, all-cause dementia; AD, Alzheimer's disease; VaD, vascular dementia; GFAP, glial fibrillary acidic protein; DHA, docosahexaenoic acid;

ROC, receiver operating characteristic; AUC, area under the curve.

Figure 2. Forest plots illustrating allele dosage-dependent associations of *APOE4* genotypes with incident ACD, AD, and VaD. Panel A presents pooled ORs and corresponding 95% CIs comparing all *APOE4* carriers against non-carriers across three dementia outcomes. Panel B further stratifies risk estimates by *APOE4* zygosity, with blue dots representing heterozygous carriers and red dots representing homozygous carriers to quantify graded genetic risk effects. All logistic regression analyses were adjusted for core demographic, lifestyle and clinical confounding factors. Bonferroni method was implemented for multiple testing corrections. **** $P < 0.0001$. Abbreviations: *APOE*, Apolipoprotein E; ACD, all-cause dementia; AD, Alzheimer's disease; VaD, vascular dementia; OR, odds ratio; CI, confidence interval.

Figure 3. Regional gray matter volume and white matter microstructural integrity as mediators linking *APOE4* to incident ACD and AD. Panels A–B report mediation estimates for bilateral hippocampal and left thalamic volumes for ACD and AD outcomes separately. Panels C–D display the mediating effects of tract-level FA in multiple white matter tracts for ACD and AD risk. Panels E–F show the mediating effects of tract-level MD in multiple white matter tracts for ACD and AD risk. All mediation models were fully adjusted for standard demographic, lifestyle and clinical confounders, with ACME effect sizes presented for each brain region. Bonferroni method was implemented for multiple testing corrections. Statistical significance thresholds are annotated as * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. The

structural brain traits with significant mediating effects were visualized via the ggseg3d package in R. Abbreviations: APOE, Apolipoprotein E; ACD, all-cause dementia; AD, Alzheimer's disease; ACME, average causal mediation effect; HCg, hippocampal cingulum; MCP, middle cerebellar peduncle; PTR, posterior thalamic radiation; ACR, anterior corona radiata; CC, corpus callosum; SCR, superior corona radiata; PCR, posterior corona radiata; SLF, superior longitudinal fasciculus.

Figure 4. The mediating roles of plasma proteins in the associations between

***APOE4* and incident ACD, AD, and VaD.** Panel A identifies a panel of significant protein mediators underlying the *APOE4*–ACD association. Panel B depicts distinct plasma protein mediators mediating the relationship between *APOE4* and AD risk.

Panel C highlights four proteins exerting significant mediating effects for VaD outcomes.

All mediation models were fully adjusted for demographic, lifestyle and clinical confounding covariates, with statistical significance annotated as $*P < 0.05$, $**P < 0.01$,

$***P < 0.001$, $****P < 0.0001$ after Bonferroni corrections. Abbreviations: APOE,

Apolipoprotein E; ACD, all-cause dementia; AD, Alzheimer's disease; VaD, vascular dementia; ACME, average causal mediation effect; GFAP, glial fibrillary acidic protein;

GHR, growth hormone receptor; VGF, VGF nerve growth factor inducible; CEND1, cell cycle exit and neuronal differentiation 1; TNFSF10, tumor necrosis factor superfamily member 10; FURIN, furin; PVR, poliovirus receptor; SYT1, synaptotagmin 1; KYNU,

kynureninase; ITGA2, integrin subunit alpha 2; MENT, serine protease inhibitor, clade A, member 3; SPON2, spondin 2.

Figure 5. The mediating roles of plasma metabolites in the associations between *APOE4* and incident ACD, AD, and VaD. Separate fully adjusted mediation models were constructed for three dementia endpoints: ACD (Panel A), VaD (Panel B), and AD (Panel C). Each panel displays the regression coefficient for the path from *APOE4* to metabolite, the regression coefficient for the path from metabolite to dementia outcome, and ACME. Statistical significance was annotated with asterisks: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ after Bonferroni corrections. Abbreviations: LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; C, cholesterol; CE, cholesteryl ester; FC, free cholesterol; PL, phospholipid; TL, total lipid; Pts, particles; *APOE4*, apolipoprotein E $\epsilon 4$ allele; AD, Alzheimer's disease; VaD, vascular dementia; ACD, all-cause dementia; ACME, Average Causal Mediation Effect. Total metabolite abbreviations are detailed in Supplementary Table 2.

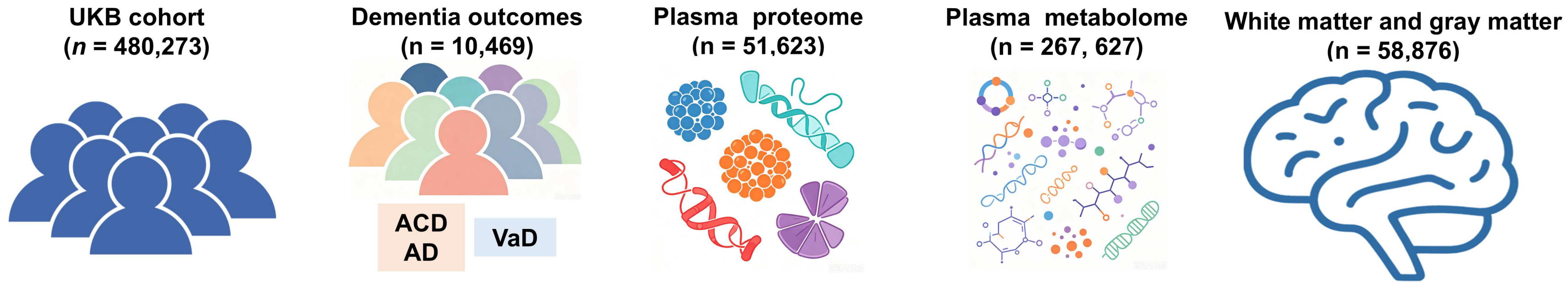
Figure 6. Protein-based predictive models for incident ACD, AD and VaD in *APOE4* heterozygotes and homozygotes. Protein signatures were selected from top outcome-specific mediators: five markers for ACD (*APOE*, GFAP, VGF, FURIN, PVR), five for AD (*APOE*, MENT, GFAP, FURIN, VGF), four for VaD (GFAP, ITGA2, PVR, SPON2). ROC curve analysis was used to assess the performance of the constructed prediction models in *APOE4* heterozygotes (A) and homozygotes (B). Corresponding AUC values are labelled for each curve. Abbreviations: ACD, all-cause dementia; AD, Alzheimer's disease; VaD, vascular dementia; AUC, area under curve; ROC, receiver operating characteristic.

Table 1. Baseline participant characteristics according to APOE genotype

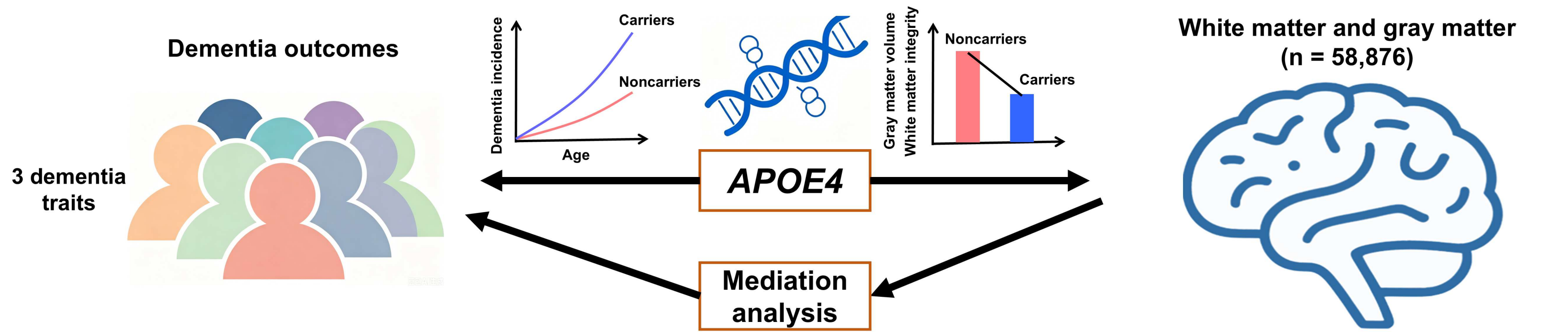
Characteristics	Overall	Non-carriers	Carriers		Heterozygotes		Homozygotes	
	N = 480,273	N = 343,812	N = 136,461	P value	N = 125,007	P value	N = 11,454	P value
Age (Years)	56.52 ± 8.09	56.55 ± 8.09	56.45 ± 8.09	<0.0001	56.46 ± 8.09	0.0003	56.36 ± 8.09	0.0119
Sex (Female)	260,819 (54.3%)	186,632 (54.3%)	74,187 (54.4%)	0.6099	67,992 (54.4%)	0.5160	6,195 (54.1%)	0.6838
Education (College or University degree)	161,593 (33.6%)	115,797 (33.7%)	45,796 (33.6%)	0.3604	41,915 (33.5%)	0.4101	3,881 (33.9%)	0.4682
Ethnicity (White)	455,465 (94.8%)	325,733 (94.7%)	129,732 (95.1%)	<0.0001	118,941 (95.1%)	<0.0001	10,791 (94.2%)	0.0133
TDI	-1.33 ± 3.08	-1.33 ± 3.07	-1.33 ± 3.09	0.0881	-1.34 ± 3.08	0.1016	-1.32 ± 3.12	0.5278
Employment status	259,522 (54.0%)	185,608 (54.0%)	73,914 (54.2%)	0.2613	67,784 (54.2%)	0.1476	6,130 (53.5%)	0.3287
Physical activity (MET-h/day)	2,647.23 ± 2,650.47	2,634.96 ± 2,644.46	2,678.14 ± 2,665.30	<0.0001	2,671.56 ± 2,664.17	<0.0001	2,750.01 ± 2,676.63	<0.0001
BMI (kg/m2)	27.41 ± 4.78	27.43 ± 4.78	27.37 ± 4.79	<0.0001	27.39 ± 4.80	<0.0001	27.16 ± 4.71	<0.0001
Smoking history	287,596 (59.9%)	206,048 (59.9%)	81,548 (59.8%)	0.2763	74,704 (59.8%)	0.2935	6,844 (59.8%)	0.7087
Alcohol history	459,571 (95.7%)	328,723 (95.6%)	130,848 (95.9%)	<0.0001	119,871 (95.9%)	<0.0001	10,977 (95.8%)	0.2584
Major metabolic disorders	35,329 (7.4%)	24,950 (7.3%)	10,379 (7.6%)	<0.0001	9,442 (7.6%)	0.0006	937 (8.2%)	0.0002
Major cardiovascular diseases	76,981 (16.0%)	54,872 (16.0%)	22,109 (16.2%)	0.0398	20,224 (16.2%)	0.0721	1,885 (16.5%)	0.1568

Continuous variables (i.e., Age, BMI) are presented as mean (SD) and compared between non-carriers and diverse carrier groups using Mann-Whitney U test. Categorical variables (i.e., Sex) are expressed as n (%), with group differences assessed by chi-square test. Abbreviations: UKB, UK biobank; SD, standard deviation; APOE, Apolipoprotein E; MET, metabolic equivalent of task; BMI, body mass index; TDI, Townsend deprivation index.

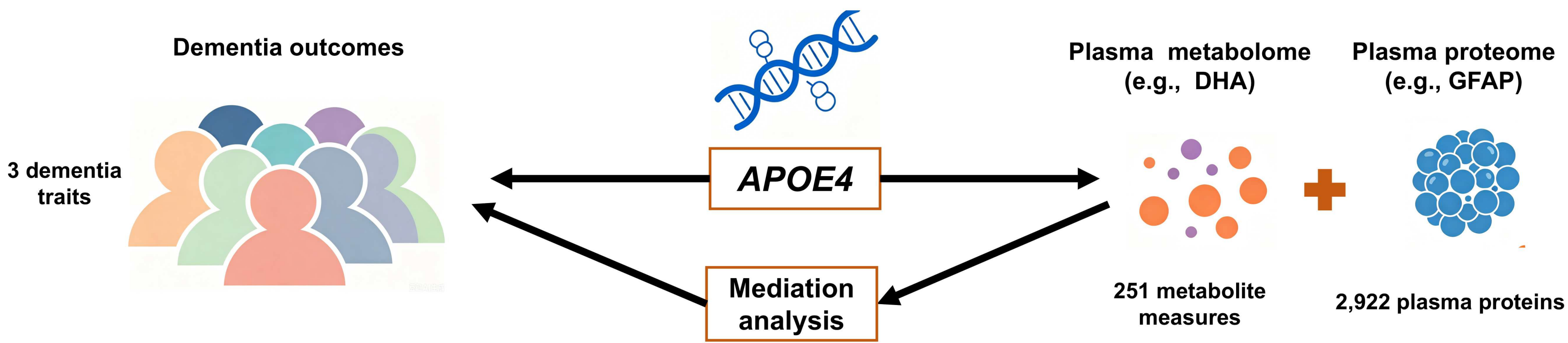
1. Study cohort and dataset



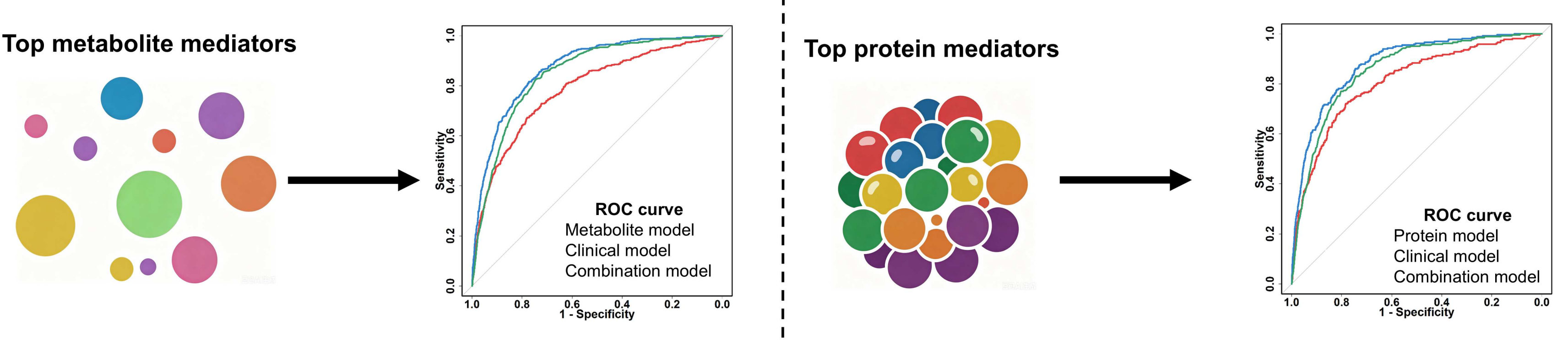
2. The mediating roles of white matter and gray matter traits in the associations between *APOE4* and incident dementia

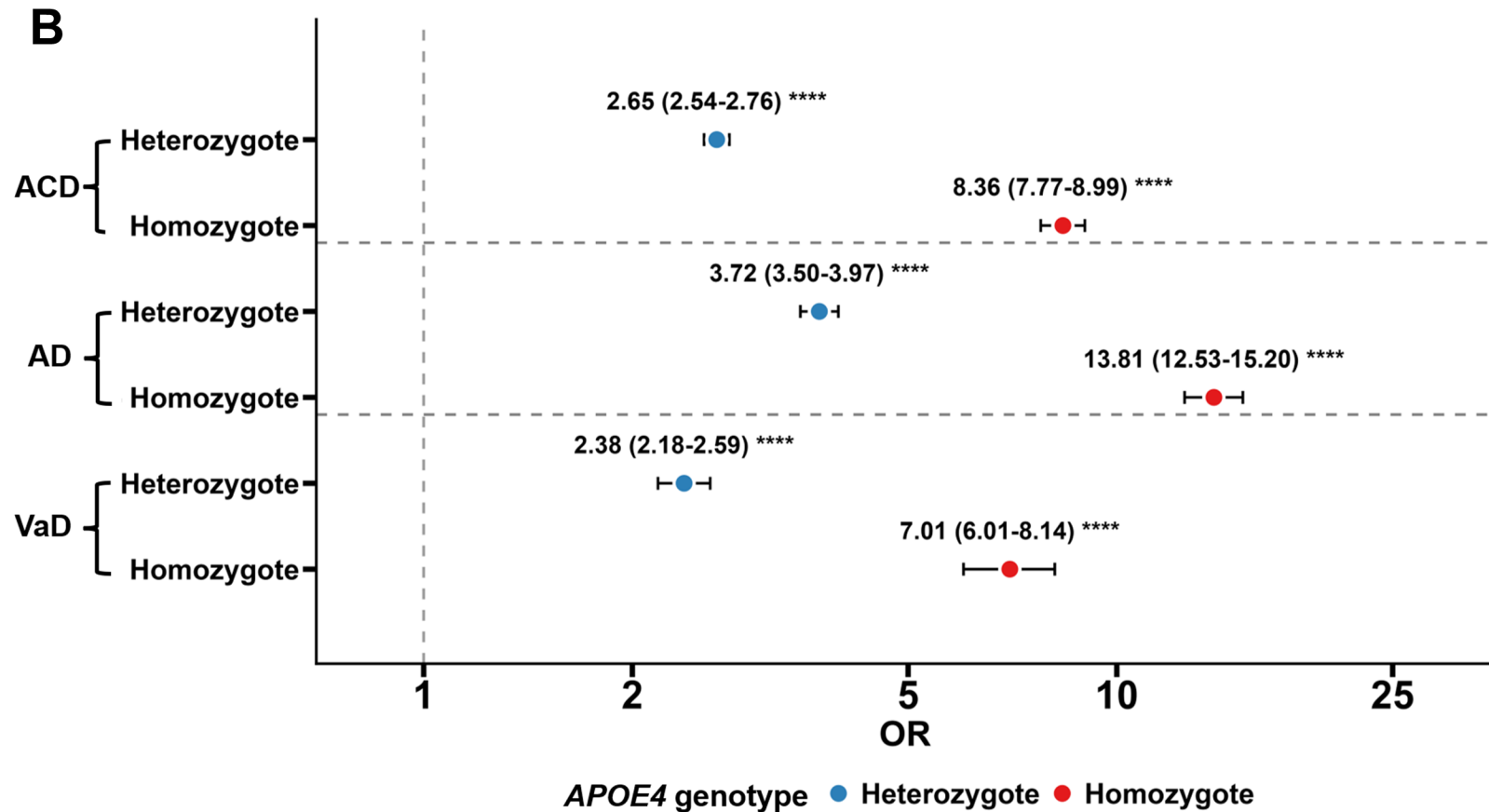
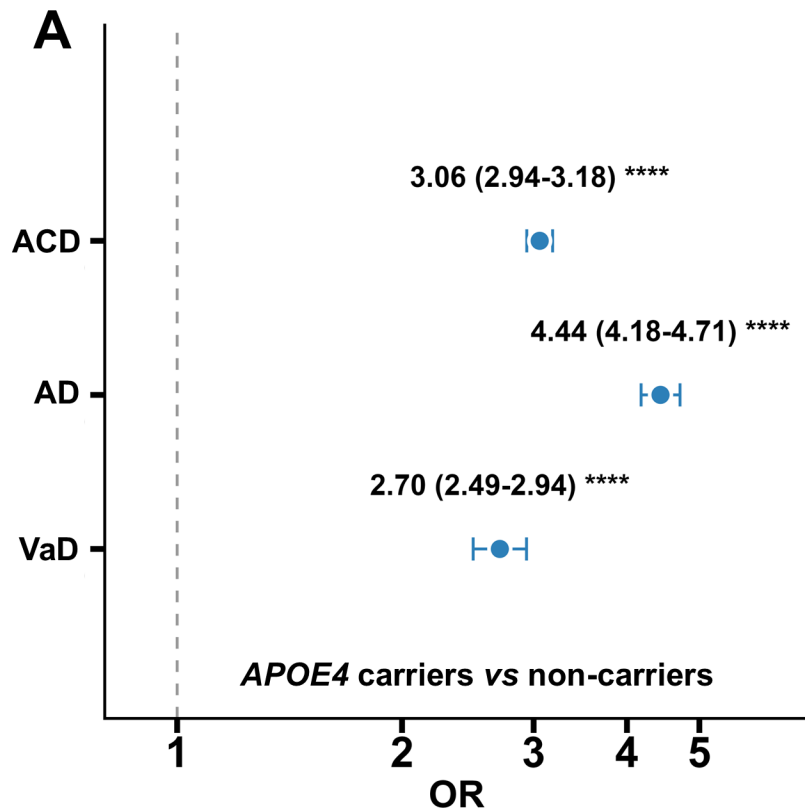


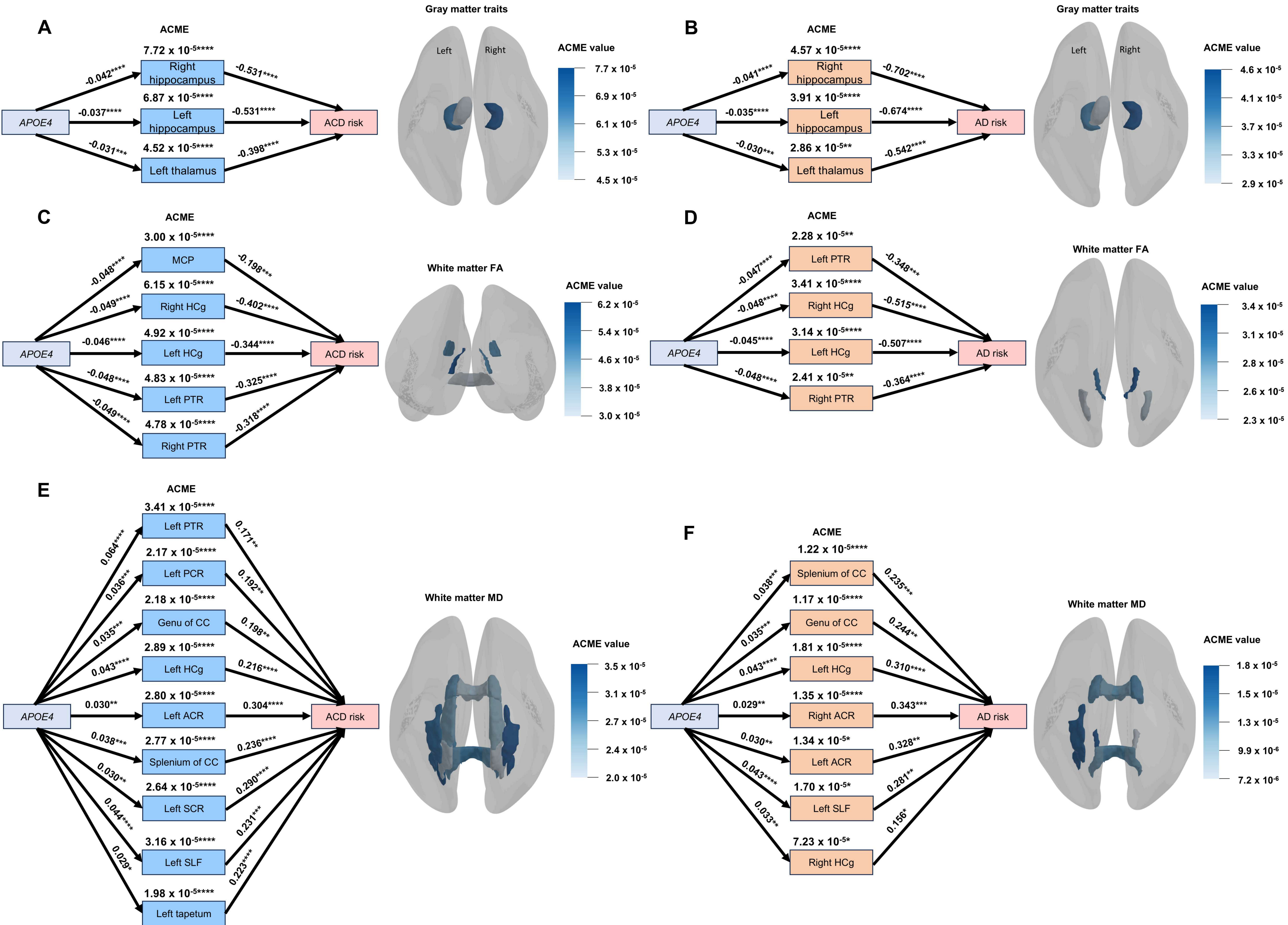
3. The mediating roles of plasma proteins/metabolites in the associations between *APOE4* and incident dementia

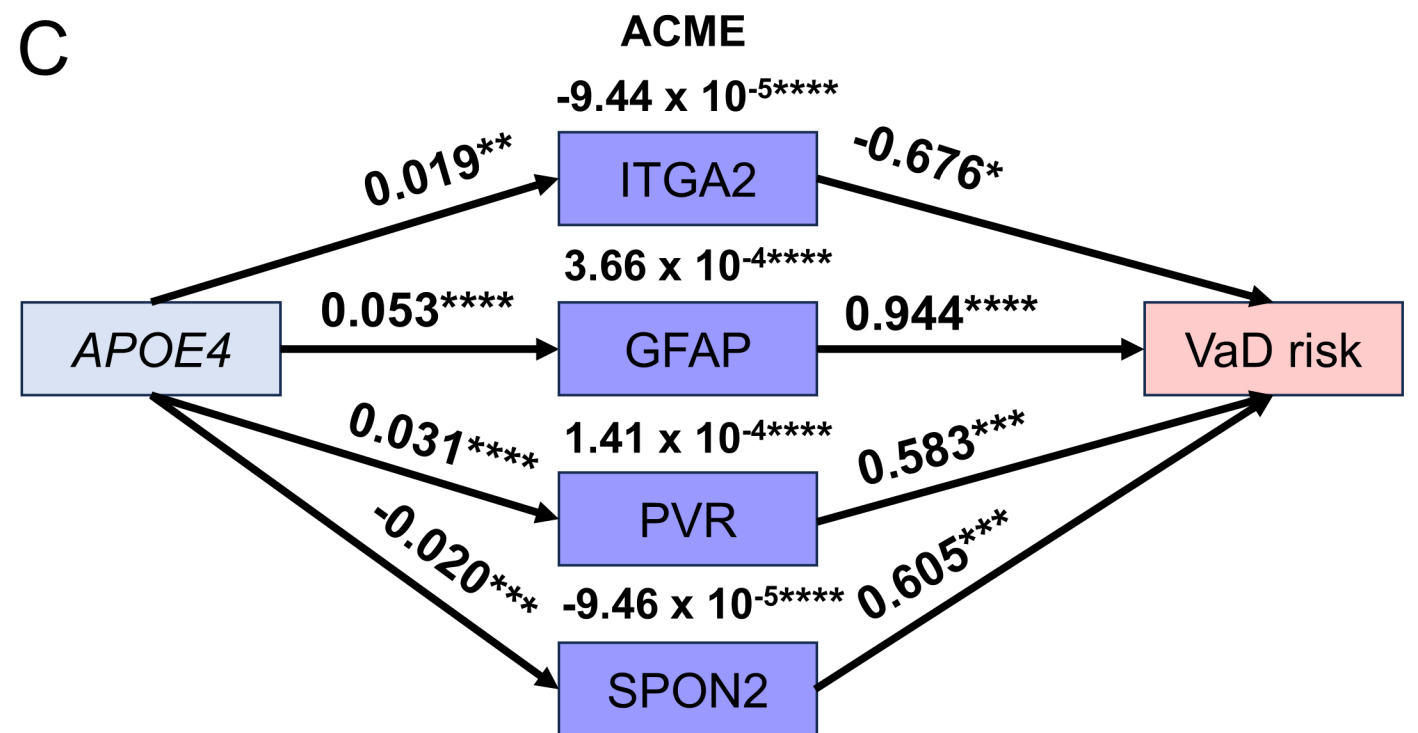
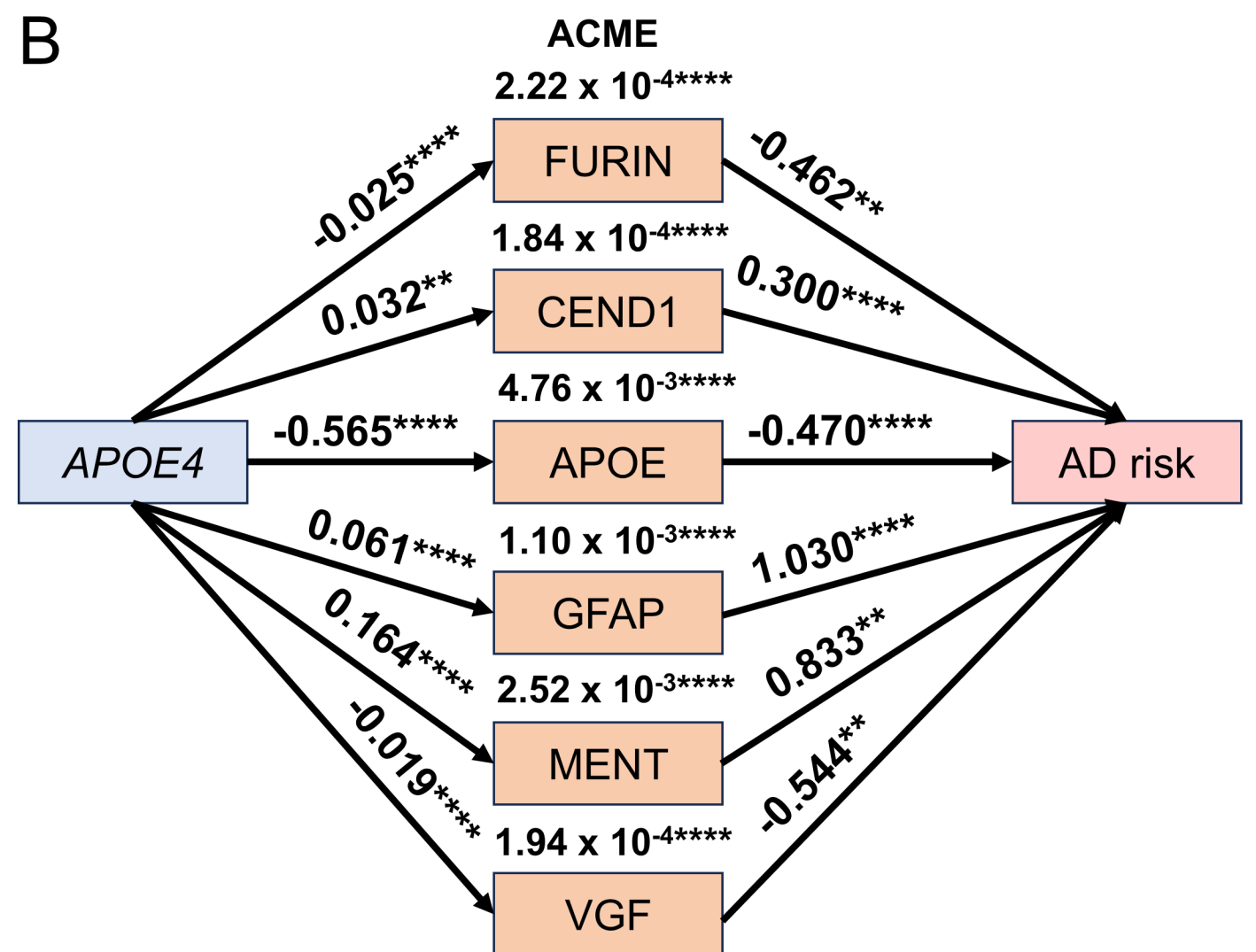
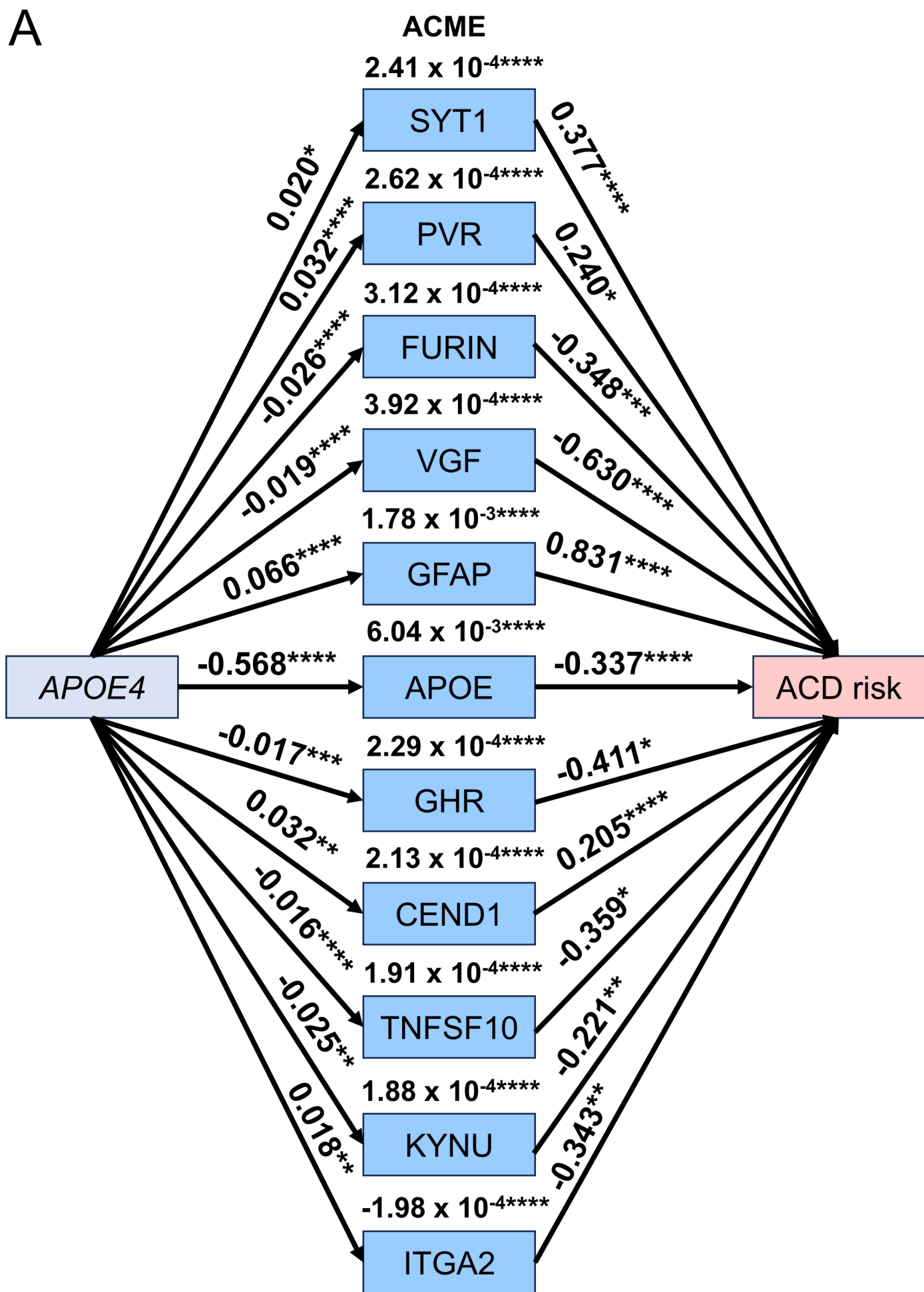


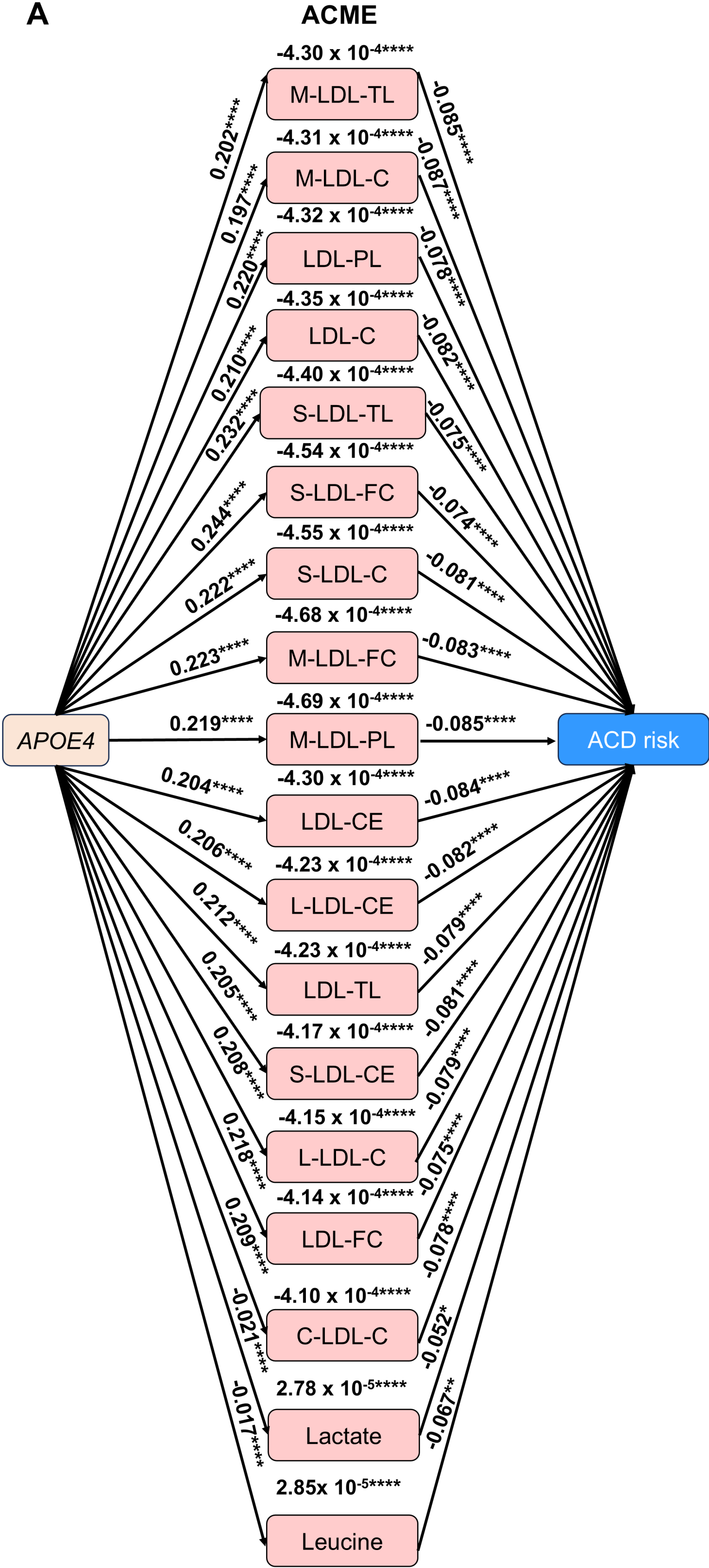
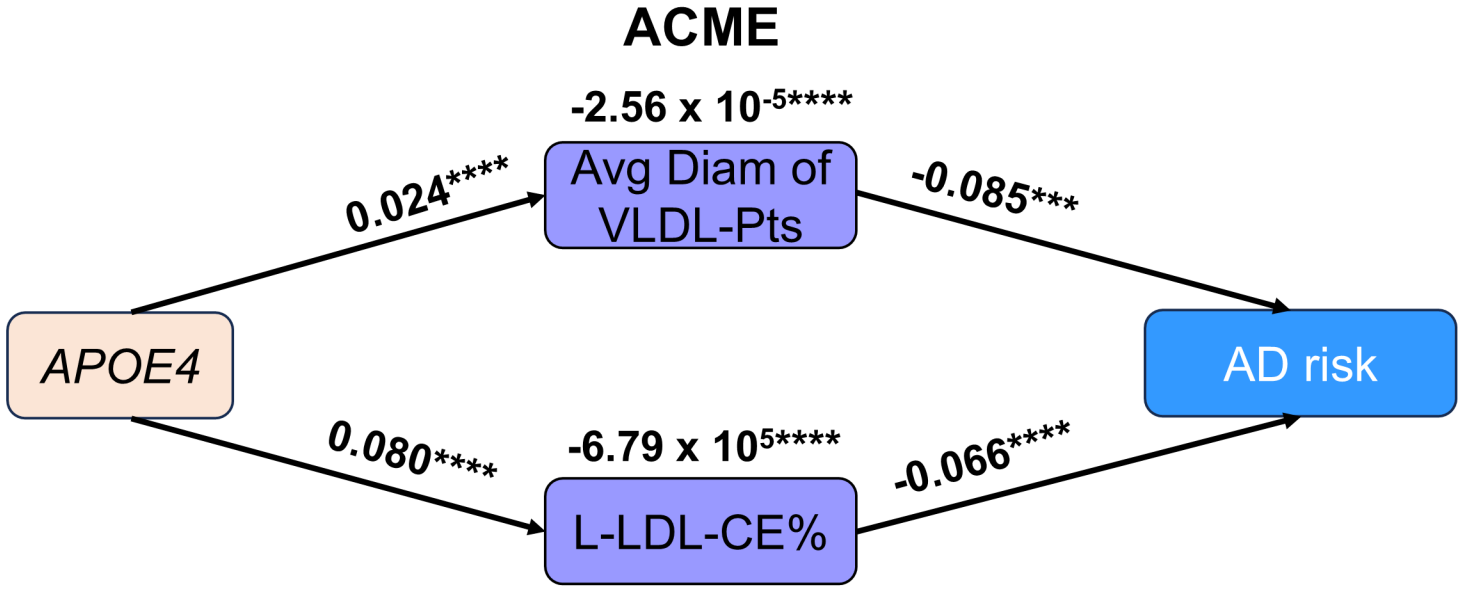
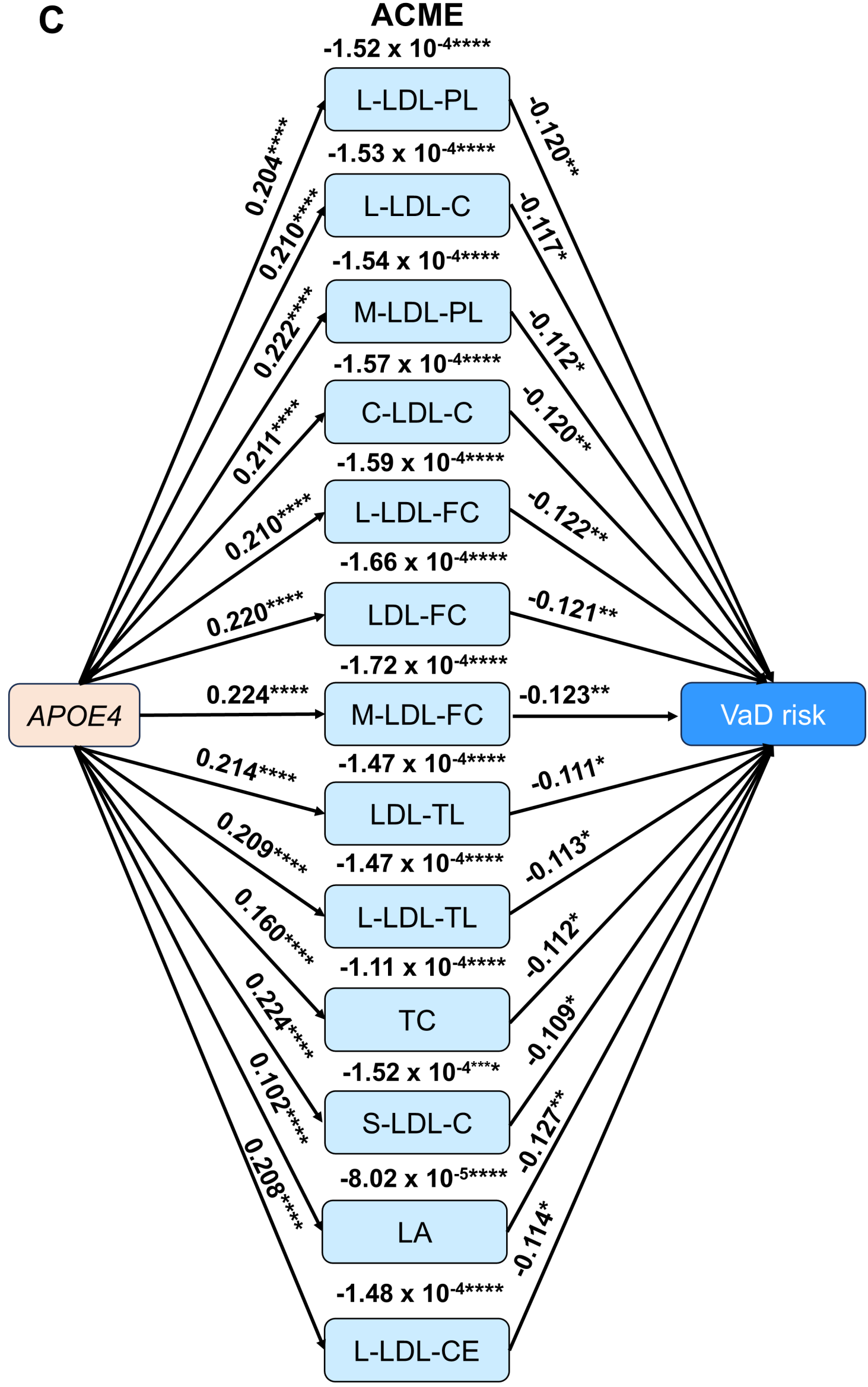
4.The predictive plasma signatures for incident dementia in *APOE4* carriers

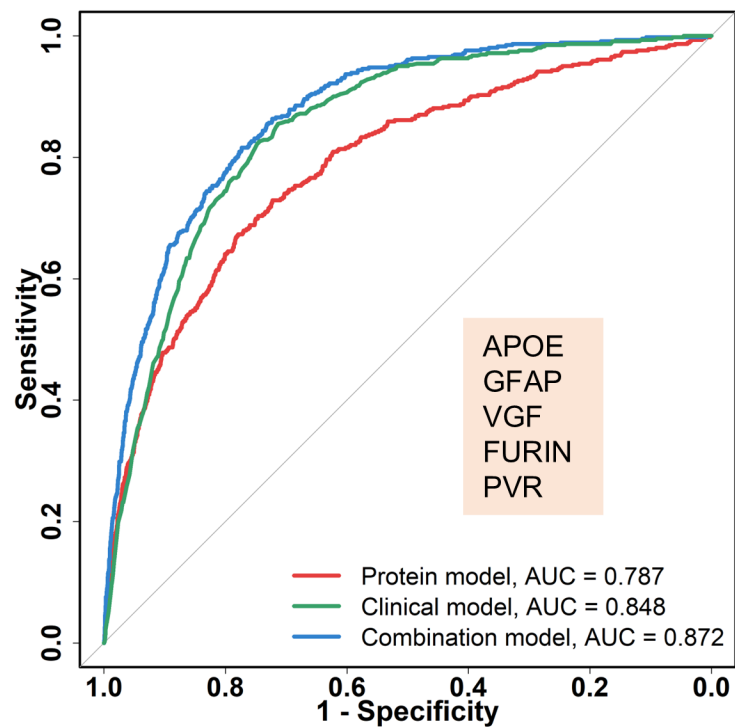
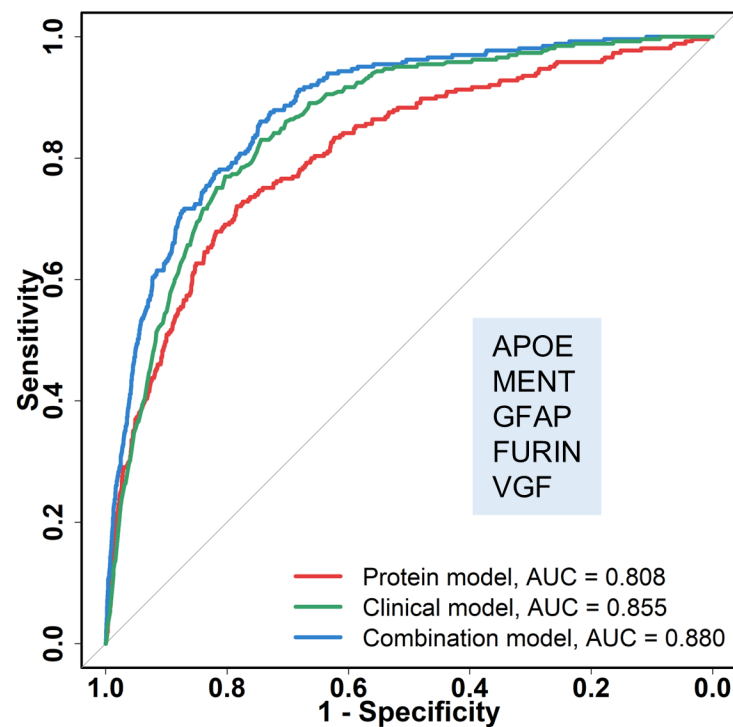
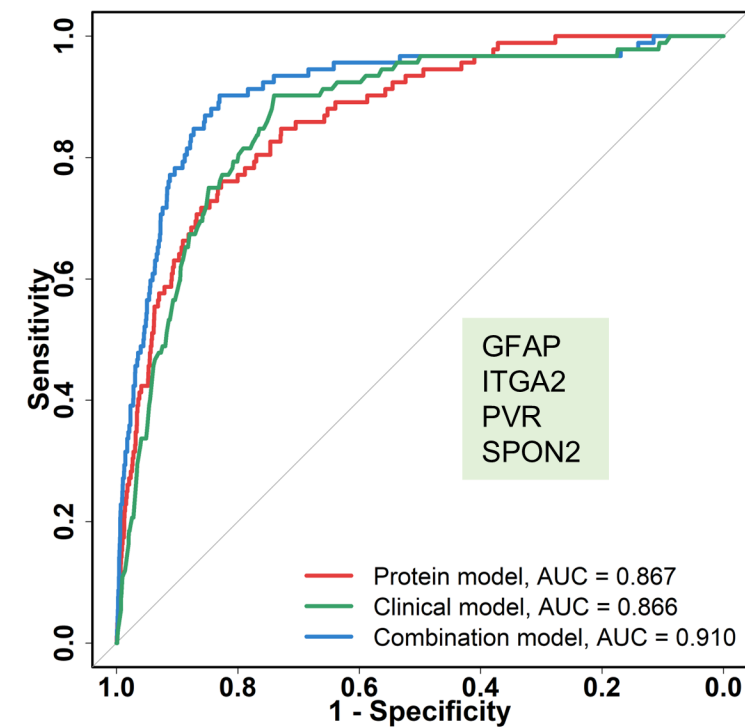
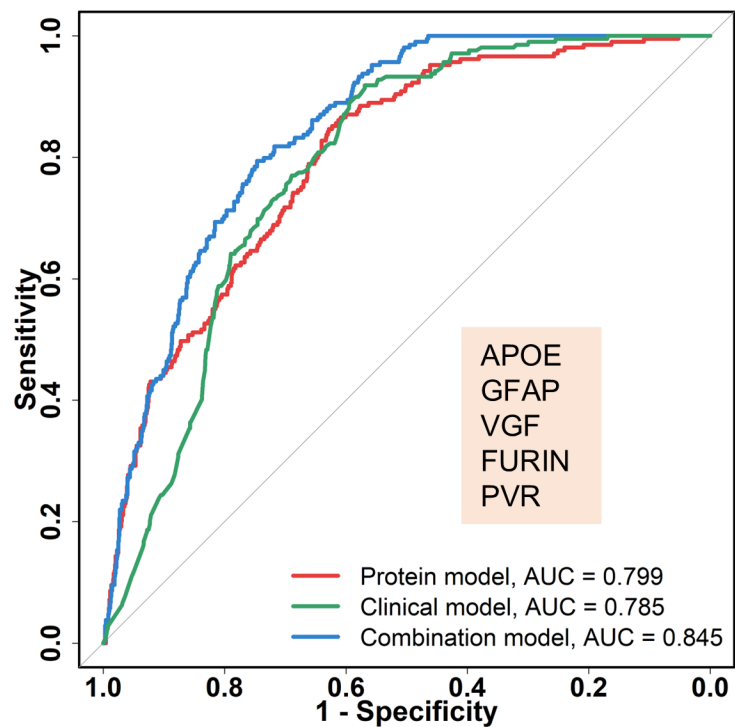
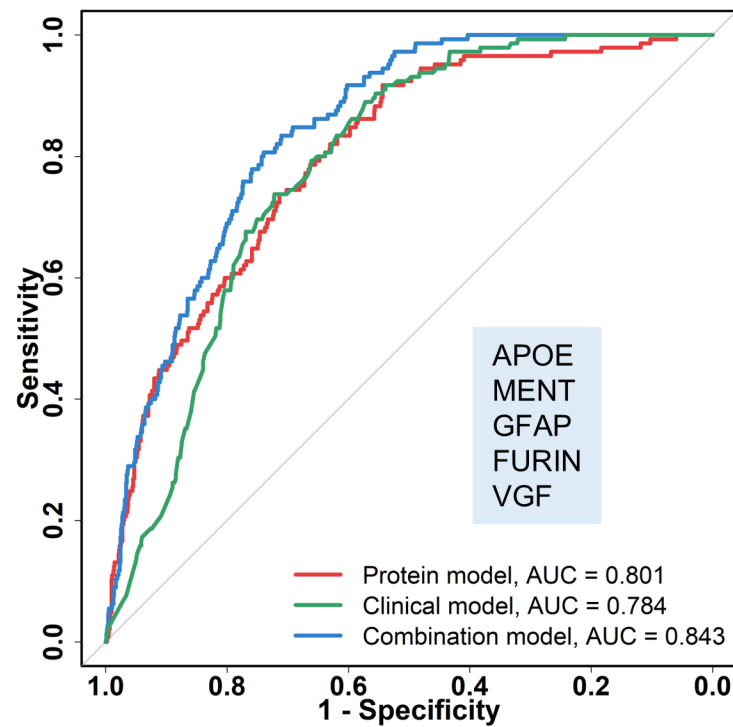
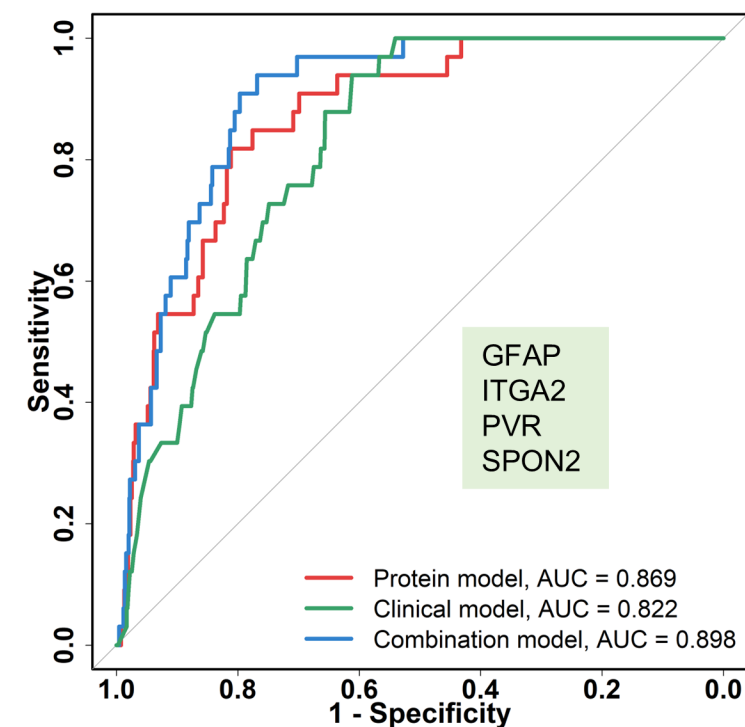








A**B****C**

A**Heterozygote****ACD****AD****VaD****B****Homozygote****ACD****AD****VaD**

Supplementary Files

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