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Association between cognitive domains and depressive symptom trajectories and their plasma proteomic correlates in a community cohort of older adults

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Abstract

Depression and cognitive decline are bidirectionally associated in older adults, but domain-specific longitudinal associations and plasma proteomic signatures remain unclear. In the Hubei Memory and Aging Cohort Study, covariate-adjusted linear mixed-effects models assessed associations between five baseline cognitive domains and depressive symptom trajectories in 2 990 community-dwelling older adults without baseline depressive symptoms (15-item Geriatric Depression Scale [GDS-15] ≤ 5); 126 (4.2%) developed new-onset symptoms. Proteomics included 1 342 participants (78 incident cases). Proteins associated with both cognitive domains and depressive symptoms underwent enrichment and protein–protein interaction analyses. Nested cross-validation evaluated regularized logistic regression using proteins selected once per outer training split; Shapley additive explanations interpreted contributions. Higher executive function (β = −0.216; 95% confidence interval [CI] − 0.414 to − 0.018) and memory function (β = −0.039; 95% CI − 0.070 to − 0.007) were associated with slower symptom progression, whereas higher visuospatial function was associated with faster progression (β = 0.054; 95% CI 0.028 to 0.079). The protective association of executive function was additionally observed among women and rural residents. Enrichment analyses linked proteins associated with memory, visuospatial ability, and executive function to humoral immunity, extracellular matrix remodeling, and cell adhesion/protein translation, respectively; antigen binding and immunoglobulin complexes were shared. Executive-domain proteins improved discrimination over the clinical model (area under the receiver operating characteristic curve [AUC], 0.814 vs. 0.787; DeLong P < 0.001); memory and visuospatial models showed no AUC improvement (DeLong P = 0.700 and 0.598). Findings suggest domain-specific trajectories, proteomic signatures, and modest predictive gains from executive-domain proteins.

Introduction

Mental health disorders among older adults have attracted increasing scientific and policy attention in the context of global population aging [1]. Late-life depression is prevalent and constitutes a substantial contributor to disability burden [2], with an estimated pooled prevalence of 31.7% [3]. Nonetheless, it remains frequently underdetected and undertreated; approximately half of affected individuals are not diagnosed [4], and significant treatment gaps persist even among those engaged with health services [5]. Consequently, enhancing the timely identification of older adults at elevated risk is a central public health objective. Depression in later life is closely associated with clinical features including memory impairment and anxiety and may contribute to accelerated functional decline and increased morbidity [6]. In the UK Biobank, depression was associated with a 51% increased risk of incident dementia, particularly among individuals exhibiting worsening or persistently severe/mild depressive symptom trajectories [7]. Evidence from the China Health and Retirement Longitudinal Study further supports bidirectional associations between cognitive functioning and depressive symptoms: poorer memory and orientation predict greater symptom worsening, with stronger coupling observed in women [8, 9]. Indicators of accelerated biological aging have similarly been linked to heightened risk of depression and anxiety [10], and patterns of cognitive change appear to predict subsequent depressive symptoms and broader health outcomes [11]. However, domain-specific associations between cognition and depression

across depressive symptom trajectories, as well as effect modification by factors such as sex and urban/rural residence, remain insufficiently characterized.

Late-life depression has multifactorial causes spanning psychosocial factors and biological pathways, including impaired neuroplasticity (e.g., altered brain-derived neurotrophic factor, hypothalamic–pituitary–adrenal axis dysregulation, chronic inflammation, and cerebrovascular lesion–related network changes [12]. Elevated inflammatory mediators are linked to neurotransmitter and behavioral changes; depression is more common in inflammatory somatic illness [13, 14], and some idiopathic major depressive disorder cases also show increased cytokines [15, 16]. Depressive symptoms in older adults, including in Alzheimer's disease (AD), may have distinct pathophysiology [17], and studies linking depressive symptoms to core AD pathology are inconsistent [18]. These findings suggest that models focused on canonical AD neuropathology or single inflammatory markers are insufficient, motivating unbiased, systems-level profiling of peripheral molecular signatures.

Plasma proteomics enables quantitative profiling of proteins spanning immune, vascular, metabolic, and neurobiological pathways. Previous studies have identified plasma protein signatures associated with risk for AD and related dementias among individuals with major depressive disorder and have derived protein-based risk scores [19]. In addition, APOE ε4–by-age interactions have been linked to metabolomic/proteomic patterns implicating ketone body utilization and branched-chain amino acid metabolism [20]. Nevertheless, the extant literature has largely emphasized global associations between depression and dementia or metabolic–genetic interactions, with comparatively limited integration of baseline cognitive domain measures, clinical characteristics, and high-throughput proteomic data to predict incident depressive symptoms.

In the present study, we investigated a cohort of community-dwelling older adults to evaluate associations between baseline cognitive subdomain performance and longitudinal trajectories of depressive symptoms. For each cognitive subdomain, exploratory analyses were conducted to identify candidate plasma proteins jointly associated with subdomain scores and depressive symptom outcomes. These findings were subsequently interrogated using functional enrichment and protein–protein interaction (PPI) analyses. We further evaluated, via nested cross-validation, whether cognitive subdomain–derived protein panels improved prediction of new-onset depressive symptoms beyond a clinical reference model incorporating demographic, lifestyle, and cardiometabolic covariates. Collectively, these hypothesis-generating analyses were designed to assess the potential incremental predictive utility of cognitive subdomain–linked plasma protein signatures.

Materials and methods

Study design and participants

The Hubei Memory and Aging Cohort Study (HMACS; registration no. ChiCTR1800019164) is an ongoing prospective cohort investigating early identification and intervention for cognitive impairment in older

adults. Multistage stratified random cluster sampling recruited permanent residents aged ≥ 60 years from urban Wuhan (31 communities in four districts) and rural Dawu County, Hubei Province (60 remote administrative villages in four townships). Sampling procedures and eligibility criteria have been reported [21–27]. The data cutoff was October 2025.

Participants were eligible if they: (1) completed the baseline assessment and at least one follow-up visit; (2) underwent multidomain cognitive testing; (3) completed a depression assessment; and (4) had data for ≥ 80% of prespecified key covariates. Exclusion criteria were: (1) severe psychiatric disorders, life-threatening major somatic illnesses, or severe sensory impairments that could preclude valid assessment; (2) relocation outside the study catchment area during follow-up; or (3) baseline depressive symptoms (15-item Geriatric Depression Scale [GDS-15] score > 5).

Of 4 041 individuals screened, 1 051 were excluded for severe mental or physical disorders (n = 248), relocation (n = 98), missing cognitive assessments (n = 572), or baseline depressive symptoms (GDS-15 > 5; n = 133). The primary analysis included 2 990 community-dwelling older adults without baseline depressive symptoms (GDS-15 ≤ 5). The proteomics subcohort comprised 1 342 participants with available baseline plasma specimens that passed quality control. The protocol was approved by the Ethics Committee of Wuhan University of Science and Technology (Approval No. 201845), and all participants provided written informed consent before enrollment.

Assessment of cognitive domains and depressive symptoms

At baseline and follow-up, physicians, medical graduate students, and researchers specializing in neuropsychiatric disorders administered a standardized in-person neuropsychological battery. Five domains were assessed: memory (Auditory Word Learning Test [AVLT]), language (Boston Naming Test), visuospatial ability (Clock Drawing Test), executive function (Connect-the-Dots Test, Part B), and attention (Digit Span Test).

Memory was the mean of z-scores for summed AVLT 7.1–7.3 and 7.4–7.5 scores, without re-standardization after averaging. Executive completion time (T, seconds) was transformed as $-\log_{10}(T)$ before z-standardization; higher values indicated better performance.

For other domains, raw test scores were converted to z-scores using baseline sample means and standard deviations. Global cognition was the mean of available domain z-scores, provided at least two domains were completed. Domain-specific sample sizes varied by test completion. Scores were used for baseline comparisons (Table 1) and longitudinal analyses (Figure. 1).

Table 1
Baseline characteristics of the study participants.

Characteristics	All (n = 2 990)	Depressive symptoms			
		No new-onset depressive symptoms (n = 2 864)	New-onset depressive symptoms (n = 126)	Statistic (χ^2/Z/t)	p-value
Demographic characteristics					
Age, years*	70.00 (67.00, 74.00)[a]	70.00 (67.00, 74.00)[a]	69.00 (66.00, 74.00)[a]	0.75[b]	0.452
Education, years*	7.00 (0.00, 12.00)[a]	7.00 (0.00, 12.00)[a]	0.00 (0.00, 9.00)[a]	4.46[b]	< 0.001
Residence (%)				22.15	< 0.001
Rural	1607 (53.7)	1513 (52.8)	94 (74.6)		
Urban	1383 (46.3)	1351 (47.2)	32 (25.4)		
Sex (%)				6.14	0.013
Male	1378 (46.1)	1334 (46.6)	44 (34.9)		
Female	1612 (53.9)	1530 (53.4)	82 (65.1)		
Health status					
Hypertension (%)	1564 (52.5)	1493 (52.4)	71 (56.3)	0.62	0.433
Diabetes (%)	517 (17.4)	483 (17.0)	34 (27.0)	7.65	0.006
Hyperlipidemia (%)	656 (22.1)	625 (22.0)	31 (24.6)	0.35	0.555
Cerebrovascular disease (%)	618 (20.9)	575 (20.3)	43 (34.4)	13.64	< 0.001
Coronary heart disease (%)	514 (17.3)	485 (17.1)	29 (23.0)	2.58	0.108
Lifestyle					
Smoking (%)	931 (31.3)	895 (31.4)	36 (28.6)	0.33	0.565

Characteristics	All (n = 2 990)	Depressive symptoms			
		No new-onset depressive symptoms (n = 2 864)	New-onset depressive symptoms (n = 126)	Statistic (χ^2/Z/t)	p-value
Drinking (%)	989 (33.4)	955 (33.7)	34 (27.0)	2.14	0.144
Baseline cognitive domains					
Memory domain# (n = 1 784)	0.42 (0.79)	0.43 (0.79)	0.29 (0.82)	1.81[c]	0.072
Executive domain# (n = 677)	0.25 (0.28)	0.25 (0.29)	0.16 (0.18)	2.64[c]	0.012
Visuospatial domain# (n = 1 497)	-0.10 (1.02)	-0.07 (1.01)	-0.40 (1.10)	2.99[c]	0.003
Language domain# (n = 2 713)	0.04 (1.00)	0.06 (1.00)	-0.23 (0.92)	4.04[c]	< 0.001
Attention domain# (n = 1 919)	0.07 (0.96)	0.09 (0.96)	-0.22 (0.96)	3.77[c]	< 0.001
Global domain# (n = 2 990)	0.02 (0.80)	0.04 (0.80)	-0.25 (0.75)	5.26[c]	< 0.001
Follow-up duration, years, median (IQR)*	2.20 (1.10, 3.87)[a]	2.15 (1.09, 3.74)[a]	2.98 (1.38, 4.16)[a]	3.195[b]	0.0014

* Skewed continuous variables are presented as median (interquartile range), and between-group comparisons were performed using the Mann–Whitney U test. # Normally distributed continuous variables are presented as mean (standard deviation), with independent sample t-test for intergroup comparisons. Categorical variables are expressed as n (%), and intergroup differences were examined via the chi-square test. a Median (interquartile range); b z statistic; c t statistic. All participants had baseline GDS-15 scores ≤ 5. New-onset depressive symptoms were defined as a GDS-15 score > 5 during follow-up. GDS-15, 15-item Geriatric Depression Scale.

DATA AVAILABILITY

The de-identified datasets analyzed during the current study are not publicly available because they contain information that could compromise participant privacy but are available from the corresponding author (Y.Z., zengyan68@wust.edu.cn) on reasonable request and upon approval by the Ethics Committee of Wuhan University of Science and Technology.

Depressive symptoms over the preceding 2 weeks were assessed using the 15-item Geriatric Depression Scale (GDS-15; range, 0–15); scores > 5 indicated clinically relevant symptoms [28]. The primary analysis included participants with baseline GDS-15 ≤ 5; incident symptoms were defined as follow-up GDS-15 > 5.

Covariates

Baseline covariates included: (1) demographic characteristics (age, sex [male/female], place of residence [urban/rural], and years of education); (2) lifestyle factors (history of smoking and alcohol consumption [yes/no]); and (3) clinical confounders (history of hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, and cerebrovascular disease [present/absent]).

Plasma proteomics analysis

Fasting venous blood was collected from all participants. Plasma was isolated by centrifugation (2 000–3 000 rpm, 10 min, 4°C), aliquoted, stored at − 80°C, and shipped on dry ice to Shanghai Baiqu Biomedical Technology Co., Ltd. for high-throughput proteomic analysis. Low-abundance proteins were enriched using nano-magnetic beads, trypsin-digested, and desalted. Equal plasma volumes from each participant were pooled as a quality control (QC) sample.

Liquid chromatography–tandem mass spectrometry (LC–MS/MS) quantification used a nano-UPLC system (Vanquish Neo, Thermo Scientific) coupled to an Astral mass spectrometer with a nano-electrospray ion source. QC samples were injected every 10–15 study samples to monitor retention-time reproducibility and instrument signal stability. Peptides (900 ng) were loaded onto an EASY 24 min-Spray™ nano-column (150 μm × 15 cm) and eluted with a linear mobile-phase gradient. Data-independent acquisition (DIA) settings: MS1 resolution, 240K; MS1 scan range, m/z 380–980; MS2 scan range, m/z 150–2 000; normalized collision energy, 25%; isolation window, 2 m/z.

Raw data were exported using Spectronaut (v19.0.240604.62635) and processed with Pulsar. Targeted qualitative identification used the UniProt Human Reference Proteome Database predicted spectral library (Homo sapiens < 20K > 9606.speclib). Peptide- and protein-level false discovery rates were controlled at < 1% in qualitative and quantitative analyses.

Statistical methods and bioinformatic analyses

Descriptive statistics

Analyses used R (version 4.4.1). Normally distributed continuous variables are reported as mean ± standard deviation and compared using independent-samples t tests; skewed variables (e.g., age and education) as median [M (P25, P75)] and compared using the Wilcoxon rank-sum test. Categorical variables are reported as frequencies (percentages) and compared using Pearson's chi-square test. Baseline cognitive scores were z-standardized before modeling.

Association analysis.

Linear mixed-effects models (LMMs) assessed associations between baseline cognitive-domain performance and depressive-symptom trajectories. Fixed effects included baseline cognition, follow-up time, and their interaction (cognition × time); random effects included participant-specific intercepts and time slopes. Models used maximum likelihood estimation with the limited-memory Broyden–Fletcher–Goldfarb–Shanno optimizer, adjusted for covariates specified in the Covariates section, and stratified by sex and residence to assess effect heterogeneity.

Sensitivity analysis.

Robustness was examined using three prespecified sensitivity analyses addressing missing covariate data, baseline depressive status, and potential survival bias

(1) multiple imputation of covariates with 0.2%–12% missingness (five datasets); (2) inclusion of 133 participants with baseline depressive symptoms (GDS-15 ≥ 6; total n = 3 123); and (3) exclusion of participants who died during early follow-up (n = 2 936). Results are reported as regression coefficients (β) with 95% confidence intervals (CIs). Tests were two-sided (α = 0.05).

Proteomics analysis.

Among 5 305 detected proteins, proteins with a coefficient of variation > 30% in quality control (QC) samples or > 20% missingness were excluded, yielding 1 879 proteins for analysis.Full-sample exploratory analyses used half-minimum imputation, followed by log2 transformation and z-standardization; prediction used the pre-imputation matrix (preprocessing described below). Separate LMMs related standardized protein abundances to cognitive-domain and depressive-symptom scores, adjusting for the covariates above. Proteins associated with both outcomes at nominal P < 0.05 (no multiple-testing correction) formed exploratory candidates for Gene Ontology (GO) enrichment and protein–protein interaction (PPI) analyses. Full-sample candidates were not prediction inputs; association screening and intersection-based selection were repeated within training partitions.

Candidate protein gene symbols were mapped to Entrez Gene IDs using $bitr$ in clusterProfiler (v4.16.0). GO enrichment used org.Hs.eg.db and Benjamini–Hochberg (BH) correction to control the false discovery rate (FDR); FDR < 0.05 defined significant terms across biological process (BP), cellular component (CC), and molecular function (MF). Full-sample candidates were queried in STRING (Search Tool for the Retrieval of Interacting Genes/Proteins; v12.0; Homo sapiens) to construct PPI networks (combined score > 0.400). Cytoscape (v3.9.1) visualized networks for identifying domain-specific core interaction modules and key nodes.

Machine learning model development

Regularized logistic regression tested whether subdomain-specific candidate proteins improved discrimination of new-onset depressive symptoms beyond prespecified clinical comparators. Three feature sets were defined per subdomain: Model 1 (M1), sex, age, and urban–rural residence; Model 2

(M2), M1 plus education, lifestyle factors, histories of five chronic diseases, and baseline z-scores for the other four cognitive subdomains; and Model 3 (M3), M2 plus training-selected proteins. The M3–M2 comparison quantified the proteins' incremental discriminative value.

Stratified five-fold nested cross-validation was repeated five times. Before tuning, protein associations with (i) cognitive subdomain scores and (ii) depressive symptoms were re-tested once per outer training partition, including its inner training and validation subsets. Proteins meeting prespecified criteria for both outcomes formed an intersection set, held fixed during inner-loop tuning and final fitting on the full outer training partition. Outer test folds were used only for performance evaluation. Inner-loop grid search tuned the regularization mixing parameter α (0, 0.5, or 1, corresponding to ridge, elastic net, or least absolute shrinkage and selection operator [LASSO], respectively) and penalty strength λ. missForest imputation and predictor standardization were fitted using training data only and applied to validation and test data without refitting.

Performance metrics included the area under the receiver operating characteristic curve (AUC), with DeLong 95% confidence intervals from pooled out-of-fold predictions; the area under the precision–recall curve (PR-AUC); Brier score; calibration slope; and sensitivity at 80% and 90% specificity. AUC differences were tested using paired DeLong tests on pooled predictions and paired Wilcoxon signed-rank tests on fold-level AUCs. Feature-selection stability was summarized by non-zero coefficient frequency across cross-validation fits; selected proteins per outer fold were reported as median (range). Shapley additive explanations (SHAP) values were computed from a full-sample model (rather than cross-validated models) and were used descriptively to summarize variable contributions, alongside exploratory PPI network findings, without inferential validation.

Results

Baseline characteristics of study participants

Table 1 summarizes baseline characteristics of 2 990 community-dwelling older adults (median age, 70.00 years [67.00–74.00]; median education, 7.00 years [0.00–12.00]; 53.9% women). All completed at least one follow-up; median follow-up was 2.20 years (IQR, 1.10–3.87 years). Among participants without baseline depressive symptoms (GDS-15 ≤ 5), 126 (4.2%) developed incident depressive symptoms during follow-up. Regarding demographic and lifestyle characteristics, compared with the non-incident group, the incident group had higher proportions of women (65.1% vs. 53.4%; P = 0.013) and rural residents (74.6% vs. 52.8%; P < 0.001), and lower median education (0 vs. 7 years; P < 0.001). Age, smoking, and alcohol consumption did not differ significantly between groups. Regarding clinical comorbidities, diabetes (27.0% vs. 17.0%; P = 0.006) and cerebrovascular disease (34.4% vs. 20.3%; P < 0.001) were more prevalent in the incident group; hypertension, hyperlipidemia, and coronary heart disease did not differ significantly. Baseline cognitive performance differed between groups. Baseline language (n = 2 713; −0.23 ± 0.92 vs. 0.06 ± 1.00) and attention scores (n = 1 919; −0.22 ± 0.96 vs. 0.09 ± 0.96) were lower in the incident group (both P < 0.001). Memory scores were numerically lower but not

significantly different (n = 1 784; 0.29 ± 0.82 vs. 0.43 ± 0.79; P = 0.072). Executive function (n = 677; 0.16 ± 0.18 vs. 0.25 ± 0.29; P = 0.012) and visuospatial function (n = 1 497; −0.40 ± 1.10 vs. −0.07 ± 1.01; P = 0.003) scores were also significantly lower. The incident group had a lower overall cognitive composite score (n = 2 990; −0.25 ± 0.75 vs. 0.04 ± 0.80; P < 0.001), indicating broadly poorer baseline cognition. The proteomics subsample comprised 1 342 participants (of N = 2 990) and was comparable to the full cohort in demographics, clinical status, and cognition (Supplementary Table S6).

LMM analyses of baseline cognitive domains and depressive symptom trajectories

After adjustment for demographic, lifestyle, and clinical covariates (Figure. 1; Supplementary Table S1) in Model 3, time effects in all five cognitive-domain models were significantly associated with increases in depressive symptom scores over follow-up. In unadjusted Model 1, higher memory, visuospatial, attention, and language scores were significantly associated with lower baseline depressive symptom levels. After full adjustment (Model 3), only visuospatial function remained independently associated with lower baseline depressive symptom levels (β = −0.151; 95% CI − 0.225 to − 0.076).

In Model 3, domain × time interactions showed that higher baseline executive function (β = −0.216; 95% CI − 0.414 to − 0.018) and memory (β = −0.039; 95% CI − 0.070 to − 0.007) were associated with slower increases in depressive symptoms, whereas higher visuospatial function was associated with faster worsening (β = 0.054; 95% CI 0.028 to 0.079). Attention and language showed trends toward slower symptom progression in Model 1, but their interactions were not statistically significant after demographic and clinical adjustment (Models 2 and 3). In Model 3, higher global cognition was significantly associated with lower baseline depressive symptom levels (β = −0.089; 95% CI − 0.139 to − 0.040), but the global cognition × time interaction was not statistically significant in the overall population.

Subgroup analysis of cognitive domains and trajectories of depressive symptoms

LMMs stratified by sex (male, female) and residence (urban, rural) assessed heterogeneity in associations between baseline cognitive domains and depressive symptom trajectories (Figure. 1G; Supplementary Table S2). Overall, higher baseline cognitive performance was significantly associated with lower baseline depressive symptom levels (β < 0). In men, higher visuospatial (β = −0.155; 95% CI, − 0.251 to − 0.058) and language scores (β = −0.083; 95% CI, − 0.154 to − 0.011) were associated with lower baseline symptoms; in women, this applied to language (β = −0.105; 95% CI, − 0.190 to − 0.021) and memory (β = −0.166; 95% CI, − 0.308 to − 0.024).

Significant domain × time associations varied by stratum. Higher baseline executive function was associated with slower symptom increases in women (β = −0.370; 95% CI, − 0.678 to − 0.063) and rural residents (β = −0.465; 95% CI, − 0.800 to − 0.129) (both β < 0). Higher baseline scores were associated with faster symptom increases (β > 0) for rural language (β = 0.164; 95% CI, 0.040 to 0.289), visuospatial

function (β = 0.365; 95% CI, 0.061 to 0.670), and memory (β = 0.156; 95% CI, 0.018 to 0.295), and for urban attention (β = 0.129; 95% CI, 0.014 to 0.243) and visuospatial function (β = 0.325; 95% CI, 0.015 to 0.634).

The baseline age × time interaction was not significant in most sex- and residence-stratified analyses; only language function in men was significant (β = 0.006; 95% CI, 0.001 to 0.011). Collectively, these results indicate that both the magnitude and direction of associations varied by sex and residence. Higher baseline executive function was consistently associated with slower worsening of depressive symptoms among women and rural older adults, whereas associations involving other cognitive domains appeared to be modified by sex and residential context.

Sensitivity analyses

Three sensitivity analyses tested the robustness of associations between baseline cognitive domains and depressive symptom trajectories using Model 3 (Supplementary Tables S3–S5). First, multiple imputation (MI) addressed missing covariates, and the linear mixed-effects model was refitted (Supplementary Table S3). Second, 133 participants with baseline depressive symptoms (GDS-15 ≥ 6) were included, with baseline symptom severity added as a covariate (total n = 3 123; Supplementary Table S4). Third, participants who died during early follow-up were excluded to address survival (attrition) bias (n = 2 936; Supplementary Table S5).

Across all analyses, executive function × time, memory × time, and visuospatial ability × time remained statistically significant and directionally consistent with the primary analysis. Higher executive function was associated with slower symptom worsening in all analyses (MI: β = −0.175; 95% CI − 0.322 to − 0.027; baseline depressive symptoms included with additional adjustment: β = −0.204; 95% CI − 0.387 to − 0.021; early deaths excluded: β = −0.205; 95% CI − 0.402 to − 0.007). Higher memory performance was likewise associated with slower worsening (MI: β = −0.041; 95% CI − 0.072 to − 0.009; baseline depressive symptoms included with additional adjustment: β = −0.040; 95% CI − 0.070 to − 0.009; early deaths excluded: β = −0.044; 95% CI − 0.076 to − 0.012). Higher visuospatial ability remained associated with faster symptom worsening (MI: β = 0.041; 95% CI 0.020 to 0.062; baseline depressive symptoms included with additional adjustment: β = 0.052; 95% CI 0.027 to 0.076; early deaths excluded: β = 0.050; 95% CI 0.024 to 0.075). Attention × time and language × time remained non-significant in all analyses.

Overall, these sensitivity analyses provide convergent evidence that the longitudinal associations of executive function, memory, and visuospatial ability with depressive symptom trajectories are robust to alternative assumptions regarding missing data, baseline depressive status, and early mortality.

Screening and functional enrichment of associated proteins

Exploratory plasma proteomics focused on memory, visuospatial ability, and executive function, the only baseline subdomains with robust, independent associations with depressive symptom trajectories. The quality-controlled dataset comprised 1 879 high-quality plasma proteins quantified in 1 342 community-

dwelling older adults from the primary sample. Covariate-adjusted LMMs identified proteins associated with each subdomain and depressive symptoms. Intersecting full-sample protein sets (Supplementary Tables S7–S9) yielded 39, 36, and 22 candidate proteins for memory, visuospatial ability, and executive function, respectively (Figure S2), for exploratory enrichment and network analyses.

GO enrichment showed distinct and shared patterns across biological process (BP), cellular component (CC), and molecular function (MF) (Figure. 2A–C). Memory proteins were enriched for adaptive immune BP terms: immunoglobulin-mediated immune responses, B-cell-mediated immunity, lymphocyte-mediated immunity, somatic recombination-based immune responses, and leukocyte-mediated immunity. CC and MF enrichment involved Ig complexes (including IgM/IgA complexes) and antigen binding, with particularly strong enrichment for both (adjusted $P = 10^{-31}$). Visuospatial proteins were enriched for ECM-related terms: extracellular matrix organization, external encapsulating structure organization, and basement membrane, plus Ig complexes and antigen binding. Executive proteins were chiefly enriched for antigen binding and Ig complexes; additional CC terms included focal adhesion, cell–matrix junctions, small cytosolic ribosomal subunits, and vesicle-associated compartments (secretory granule lumen, azurophil granule lumen, vacuolar lumen). Enrichment centered on CC and MF, with no statistically significant BP enrichment.

The comparison bubble plot (Figure. 2D) showed immune-related processes in memory and ECM/external-structure terms in visuospatial ability. Antigen binding and Ig complexes were shared across domains; blood microparticle enrichment occurred in executive and memory domains. These descriptive profiles suggest shared and domain-specific signatures involving immune activity and the extracellular microenvironment, but do not establish causal pathways linking cognition to subsequent depressive symptom progression.

PPI Network analysis of overlapping candidate proteins.

Subdomain-specific protein–protein interaction (PPI) networks were constructed from publicly annotated candidates (Figure. 2E–G). Executive, memory, and visuospatial networks contained 6, 6, and 13 nodes and 7, 5, and 10 edges, respectively. Solid and dashed edges denote high-confidence (combined score ≥ 0.7) and medium-confidence interactions (0.4 ≤ score < 0.7), respectively. In the executive network, RPS8, RPS9, and EIF2S2 formed a fully connected triad with three high-confidence edges, linked to HNRNPK–PRKCD via EIF2S2–PPP1CB. In memory, IGHV3-15, IGHV3-11, and LZTFL1 formed an interconnected module, CYFIP1 linked to IGHV3-11, and ADIPOQ–GOT2 formed a separate module; all five edges were medium-confidence. In visuospatial, FMOD, FBLN1, NID2, THBS2, and OMD formed an ECM cluster with one high-confidence edge (FMOD–OMD); the remaining edges were medium-confidence. Other modules comprised EIF2S2 connected to RPL13 and SELENOP, CAMP–SERPINA1–PROC, and ACP1–LDHA. The visuospatial network had four high-confidence interactions: FMOD–OMD, EIF2S2–SELENOP, EIF2S2–RPL13, and PROC–SERPINA1.

The integrated network contained 24 nodes and 22 non-redundant edges (Figure. 2H). EIF2S2, the only shared protein, connected the executive network (RPS8, RPS9, PPP1CB) to the visuospatial network

(RPL13, SELENOP), bridging both structures (Figure. 2H). Memory-associated proteins formed an isolated component without detected cross-subdomain interactions. Thus, subdomain networks were largely segregated, with limited executive–visuospatial overlap mediated by EIF2S2 and connectivity concentrated in a few hub proteins.

Machine learning models and feature interpretation

To complement the exploratory GO enrichment and PPI analyses, we performed predictive modeling to evaluate whether subdomain-specific protein candidate sets derived exclusively from the training data improved discrimination of incident depressive symptoms during follow-up. For each cognitive subdomain, candidate proteins were selected once within the corresponding outer training split (before hyperparameter tuning) using only training observations; the resulting protein set was then held constant throughout tuning and final model estimation, and discrimination was assessed in the held-out outer test split.

We compared three nested models: M1 (demographic), including sex, age, and urban/rural residence; M2 (clinical), comprising M1 plus years of education, smoking status, alcohol consumption, histories of five chronic conditions (hypertension, diabetes, coronary heart disease, hyperlipidemia, and cerebrovascular disease), and baseline z-scores for the remaining four cognitive domains; and M3 (combined), comprising M2 plus the proteins selected in the training split. Model performance was summarized using the AUC, and AUCs were contrasted across model specifications (Figure. 3A–C).

For the executive subdomain, AUCs were 0.814 (M3), 0.772 (M1), and 0.787 (M2); the AUC increment for M3 relative to M2 was 0.027 (DeLong $P < 0.001$; fold-level paired Wilcoxon $P < 0.001$; BH-adjusted Wilcoxon $P = 0.001$). In contrast, AUCs for M1, M2, and M3 were 0.701, 0.714, and 0.710 for memory and 0.713, 0.739, and 0.723 for visuospatial ability, respectively. Consistent with these point estimates, inclusion of proteins did not improve AUC beyond M2 for memory (DeLong $P = 0.700$; BH-adjusted Wilcoxon $P = 0.791$) or visuospatial ability (DeLong $P = 0.598$; BH-adjusted Wilcoxon $P = 0.833$). Complete model comparisons are provided in Supplementary Table S11. Because repeated cross-validation induces statistical dependence across folds, P values were interpreted descriptively rather than inferentially.

Additional performance metrics (Supplementary Table S10) indicated that, for the executive subdomain, M3 outperformed M2 with respect to PR-AUC (0.382 vs. 0.337) and sensitivity at 90% specificity (0.492 vs. 0.390). To characterize model drivers, SHAP summary (beeswarm) plots were used to rank the top 10 features by contribution for each combined model (Figure. 3D–F). Hyperlipidemia and coronary heart disease were among the top 10 predictors across all three models, while diabetes mellitus ranked in the top 10 in the executive and memory models. Prominent protein features included C4BPA, IGHV3-48, and IGHV3-7 for memory; PFKL, CSF1, RPS9 (ribosomal protein), and IGKV3-20 for executive function; and SHBG, SERPINE1, GIP, F13A1, GPX1, DCD, and MMRN1 for visuospatial ability. These predictive signals were interpreted alongside the exploratory protein association results, GO enrichment outputs, and PPI network analyses to evaluate biological concordance. Nonetheless, SHAP-derived importance rankings

and discrimination statistics should not be construed as validation of protein–protein interactions or as evidence of causal mechanisms.

Discussion

Leveraging prospective follow-up data and plasma proteomic profiling from the HMACS cohort, we investigated differential associations between baseline performance across cognitive subdomains and subsequent trajectories of depressive symptoms among community-dwelling older adults. Higher baseline executive function and memory performance were associated with attenuated increases in depressive symptom severity over time, whereas higher visuospatial performance was associated with more rapid increases. Effect modification analyses suggested heterogeneity by sex and urban–rural residence; specifically, the putative protective association of executive function was strongest among women and participants residing in rural areas.

In exploratory analyses, we conducted protein–phenotype association testing and applied pathway enrichment and PPI analyses to characterize peripheral proteomic signatures corresponding to distinct cognitive subdomains. Internal prediction analyses indicated that an executive-subdomain–informed protein selection approach yielded only modest improvements in discrimination relative to a pre-specified clinical comparator, underscoring the need for external validation to establish incremental predictive value.

Most prior longitudinal studies have primarily evaluated depressive symptomatology as a predictor of subsequent cognitive decline [29]. In contrast, the present study reversed this analytic direction and integrated plasma proteomic data. Relative to earlier reports, the current study provides several methodological advantages: (i) a substantially larger community-based sample (n = 2 990) compared with 276 in Gatchel et al. [30], 333 in Pietrzak et al. [31], and 105 in Caprioglio et al. [32]; (ii) domain-specific assessment across five cognitive domains rather than reliance on a single global cognition measure; (iii) longitudinal modelling of depressive symptom trajectories rather than cross-sectional depressive outcomes; (iv) pre-specified subgroup analyses by sex and urban versus rural residence; and (v) integration of exploratory proteomic characterization with internal predictive modelling. Collectively, this design extends prior clinically oriented observations by linking cognitive-subdomain associations to candidate peripheral protein features and by quantifying their potential predictive utility.

The observed positive association with visuospatial performance accords with the neuropathological heterogeneity described in Lewy body dementia and atypical AD [33, 34]. However, because dementia subtype adjudication and neuropathological biomarkers were not available in the present cohort, this result should be interpreted as hypothesis-generating rather than confirmatory. The absence of longitudinal associations for language and attention may be attributable to limited measurement sensitivity, reduced effective sample size, and intercorrelations among cognitive domains. The relatively stronger protective association observed for executive function among women and rural residents may reflect a combination of biological and sociocultural mechanisms. In women, postmenopausal

endocrine alterations and a higher systemic inflammatory burden may diminish neurophysiological reserve during cognitive decline [35]. In rural populations, urban–rural disparities in social support may increase vulnerability [36]. These subgroup-specific patterns extend prior evidence [37] and complement cross-sectional findings on urban–rural differences [38] by contextualizing these disparities within longitudinal trajectories of depressive symptoms. Sensitivity analyses corroborated the robustness of the primary associations (Supplementary Tables S3–S5).

At the molecular scale, the three cognitive domains displayed distinct peripheral proteomic profiles. Proteins associated with memory performance were enriched for humoral immune pathways, including IGHV family members (e.g., IGHV3-11), consistent with accumulating evidence linking immune dysregulation to AD and suggestive of a shared immunopathological axis with depression [39–41]. Proteins associated with visuospatial performance were enriched for ECM remodeling processes and formed a network centered on FMOD and FBLN1; such ECM perturbations may index microvascular and blood–brain barrier alterations relevant to atypical dementia phenotypes [42, 43]. Proteins associated with executive function implicated focal adhesion and ribosomal translation pathways, with notable contributions from RPS8 and RPS9. Prior studies have reported prefrontal abnormalities in ribosomal and adhesion-related biology in depression, and adhesion-mediated signaling may regulate translation through mechanistic target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways, supporting the plausibility of coupled pathological mechanisms [44, 45]. A similar bidirectional association between executive function and depressive symptoms has also been demonstrated in prospective analyses [46].

Nested cross-validation was used to quantify the incremental predictive value of training-derived candidate protein sets for each cognitive domain. For the executive domain, the combined model yielded an AUC of 0.814 compared with 0.787 for the prespecified clinical comparator; SHAP-based feature ranking prioritized RPS9, PFKL, and CSF1, mapping to ribosomal biology, energy metabolism, and myeloid growth-factor signaling, respectively [46–49]. By contrast, protein selection for the memory and visuospatial domains did not increase AUC beyond their respective comparator models, highlighting the difference between population-level association signals and individual-level discriminative performance, as well as the risk of overfitting when high-dimensional omics predictors are fit with limited outcome events [50, 51]. Notably, these analyses evaluate the predictive performance of the selection and modeling pipeline and do not constitute direct validation of the fixed full-sample protein lists or the inferred PPI relationships.

This large, prospective, community-based cohort study integrated multidimensional cognitive assessment, longitudinal trajectories of depressive symptoms, and plasma proteomic profiling. The application of linear LMMs, together with sensitivity analyses, supported the robustness of the findings. Subgroup analyses indicated a potentially elevated risk among women and rural residents. Key limitations include the relatively short follow-up period; modest differences between the proteomic subsample and the full cohort; the low completion rate for the executive-function test, which may have introduced selection bias; reliance on nominal, exploratory P values; a limited number of incident

outcomes relative to the number of proteins evaluated; and the absence of targeted assays and external validation. Notwithstanding these constraints, proteins implicated in humoral immune processes, ECM remodeling, and executive-function subdomains were identified as peripheral candidates warranting replication and further mechanistic investigation.

Declarations

COMPETING INTERESTS

The authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

Dr Zeng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LTY; acquisition, analysis, or interpretation of data: LTY; drafting of the manuscript: LTY, ZZW, YZ; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: LTY; visualization of the manuscript: LTY; obtained funding: YZ; supervision: YZ.

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Figures

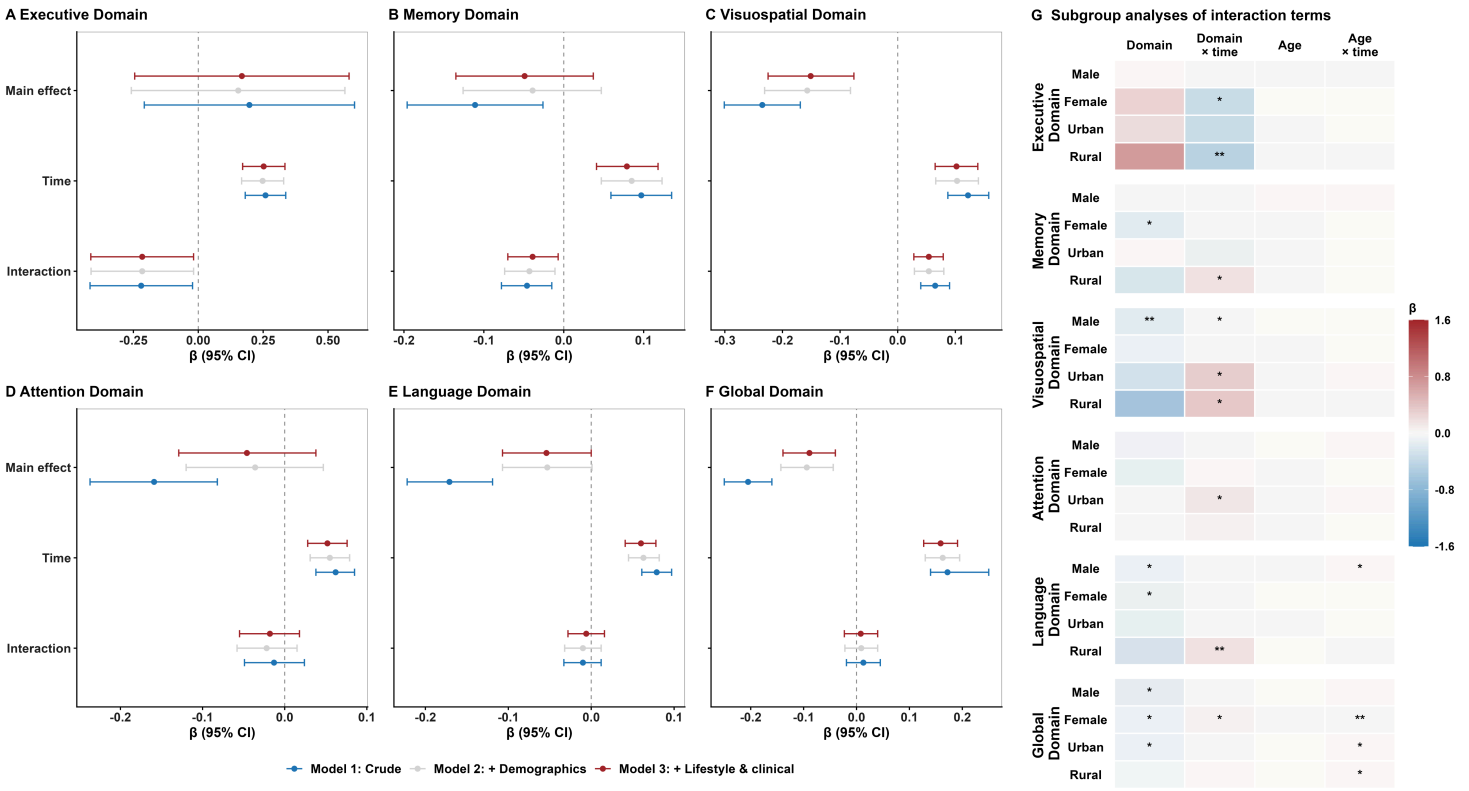


Figure 1

Associations between baseline cognitive function and longitudinal trajectories of depressive symptoms, including subgroup analyses. Panels A–F present β coefficients and 95% confidence intervals (CIs) derived from linear mixed-effects models evaluating five cognitive domains and global cognition, incorporating main effects, time effects, and cognition × time interaction terms. Model 1 (blue) is unadjusted; Model 2 (grey) is adjusted for age, sex, educational attainment, and residence; Model 3 (red) is additionally adjusted for alcohol use, smoking status, hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, and cerebrovascular disease. Dashed reference lines denote β = 0, and x-axis scales differ across panels. Panel G displays stratified coefficients by sex and residence. Color coding indicates the direction of association (blue, negative β; red, positive β), with darker shading corresponding to larger absolute effect sizes (common scale: −1.6 to 1.6). Asterisks denote statistical significance within subgroups (*P < 0.05, **P < 0.01, ***P < 0.001) and do not indicate between-subgroup differences. Complete estimates and further details regarding covariate adjustment are provided in Supplementary Tables S1 and S2.

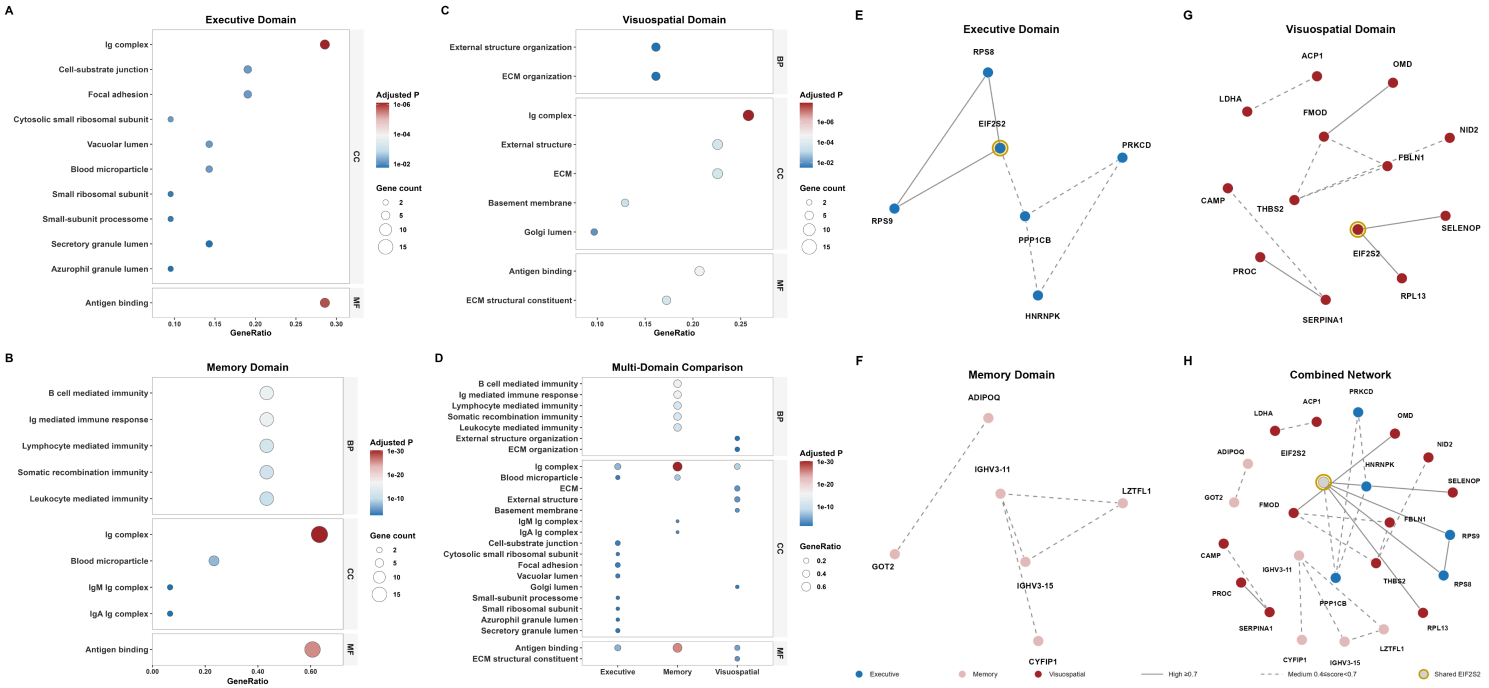


Figure 2

Gene Ontology (GO) enrichment analysis and protein–protein interaction (PPI) network visualization of plasma proteins associated with cognitive domains. (A–C) GO enrichment results for executive, memory, and visuospatial domains, respectively, were generated using clusterProfiler with Benjamini–Hochberg correction for multiple testing. The x-axis denotes the GeneRatio, and bubble area reflects the number of genes mapped to each term. (D) Cross-domain comparison of enriched GO terms, with bubble area indicating GeneRatio. Color intensity from blue to red indicates decreasing adjusted P values (increasing statistical significance). Panels A–C are displayed with domain-specific color scales, whereas panel D uses a common scale. (E–G) STRING-based protein association networks corresponding to panels A–C; (H) integrated network across domains. Edges represent STRING combined scores, with solid lines indicating scores ≥ 0.7 and dashed lines indicating 0.4 ≤ score < 0.7. Nodes are colored by domain membership (blue, executive; pink, memory; red, visuospatial). EIF2S2, shared by the executive and visuospatial domains, is emphasized with a gold outline and is rendered in gray in panel H. All nodes are displayed at uniform size. Abbreviations: BP, biological process; CC, cellular component; MF, molecular function; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

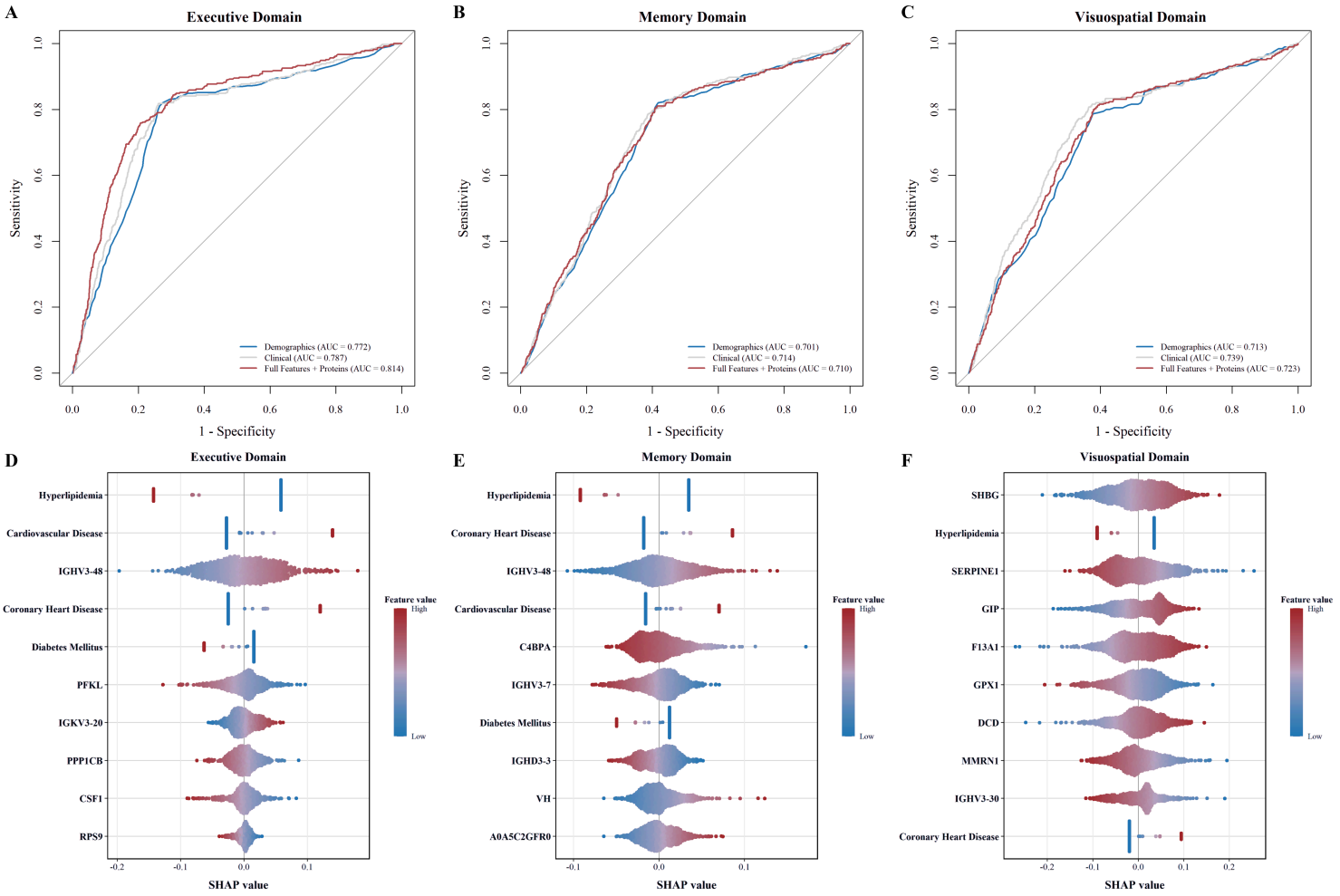


Figure 3

Internal predictive performance and Shapley additive explanations (SHAP) for protein-based models related to cognitive subdomains. Panels A–C present receiver operating characteristic (ROC) curves for the executive, memory, and visuospatial subdomains, respectively. Model M1 included sex, age, and urban/rural residence. Model M2 additionally incorporated education, lifestyle-related variables, histories of five chronic diseases, and the remaining cognitive subdomain scores. Model M3 further incorporated candidate proteins selected within the corresponding outer training partition. Within each outer training partition, association testing for cognition and depressive symptoms, intersection-based protein selection, imputation, and standardization were conducted once prior to hyperparameter optimization; the inner cross-validation loop was used exclusively for hyperparameter evaluation, and the held-out outer test set was used for performance assessment. Panels D–F display SHAP beeswarm plots for the 10 highest-ranking features in the respective combined models. The x-axis indicates each feature's contribution to the model output; red and blue denote higher and lower feature values, respectively. SHAP characterizes model behavior and does not infer causality or validate protein–protein interaction (PPI) relationships. The outcome was incident depressive symptoms during follow-up among participants with baseline GDS-15 scores ≤ 5. Comprehensive performance metrics and reported comparisons are provided in Supplementary Tables S10 and S11. GDS-15, 15-item Geriatric Depression Scale; PPI, protein–protein interaction.

Supplementary Files

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- SupplementaryTables.docx