

Plasma-Derived Proteomic Risk Score for Alzheimer’s Disease: Preliminary Results on Diagnostic Classification, Cognition and Biomarker Correlates of Significance to AD in ADNII

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Background

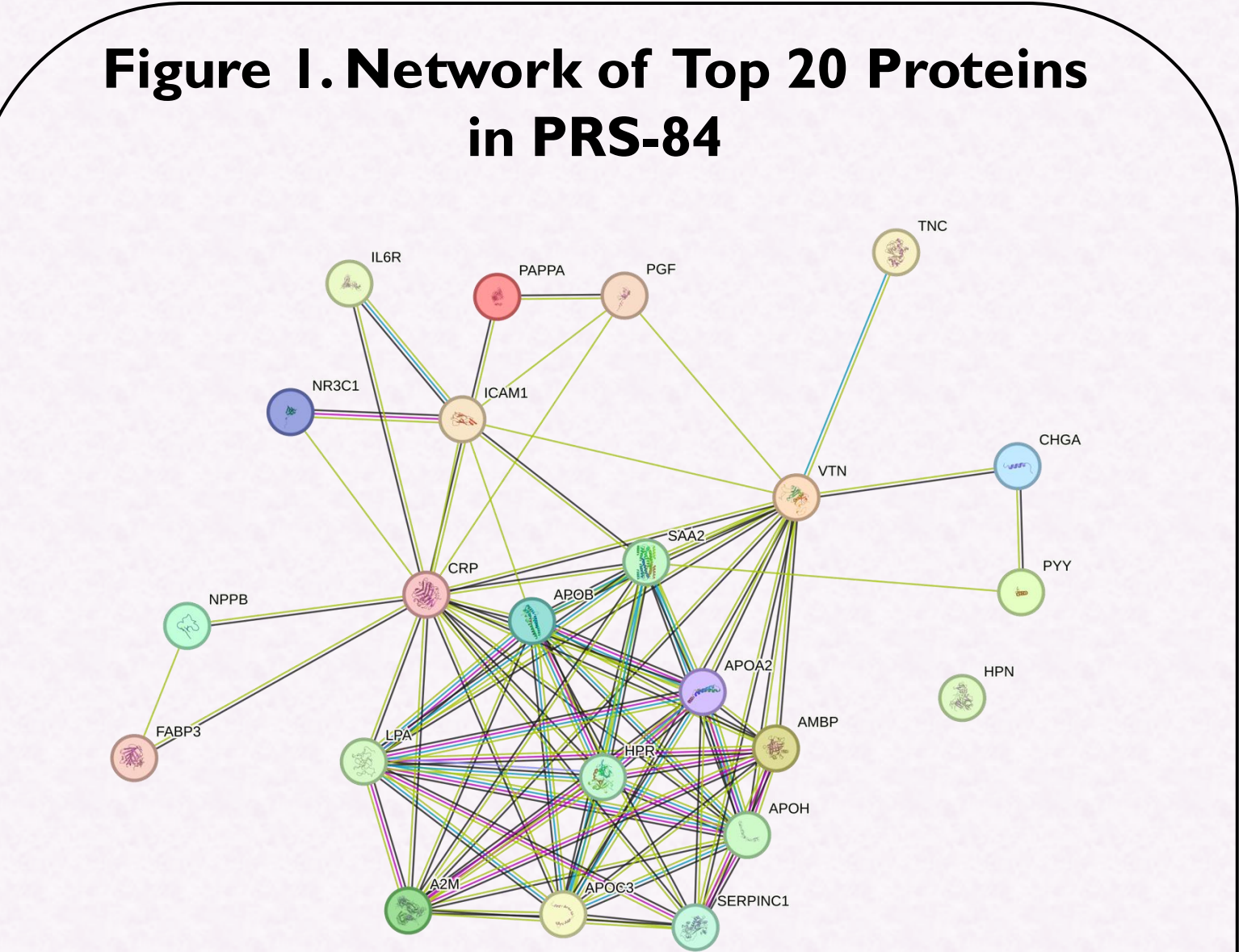
- The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a multicenter longitudinal study identifying imaging, cerebrospinal fluid (CSF) and blood biomarkers for early detection and monitoring of Alzheimer’s disease (AD).
- Proteomic profiling is a well-established method for capturing biological processes underlying AD.
- Few studies have focused on developing a plasma-derived proteomic risk score (PRS) capable of distinguishing cognitively unimpaired (CU) individuals from those with mild cognitive impairment (MCI) or dementia.
- We aimed to derive a PRS using targeted plasma proteomics from Alzheimer’s Disease Neuroimaging Initiative Phase I (ADNII) and examined its associations with diagnosis, cognitive performance and AD-relevant CSF biomarkers.

Methods

- ADNII sample (N=566; Mean_{AGE}=75 years, 38% female,10% CU, 70% MCI, and 20% Dementia) was split into training (70%; n=395) and test (30%; n=171) sets.
- Diagnosis (CU, MCI, Dementia) was modeled using elastic-net ordinal regression with plasma proteins and nested cross-validation.
- PRS was derived using elastic-net weights, and test-set receiver operating characteristic (ROC) curves assessed diagnostic discrimination.
- Gene ontology analyses characterized biological processes among PRS proteins.
- PRS associations with cognitive test performance and CSF biomarker concentrations were assessed using covariate-adjusted linear models with HC3 robust errors and FDR correction.
- Sensitivity analyses assessed PRS robustness and generalizability.

Results

Elastic net regularization analysis retained 84 out of 146 proteins in the final PRS model (PRS-84). Top 20 proteins are shown in Figure 1 and in Table 1. PRS showed moderate-to-strong diagnostic discrimination across all contrasts, clearly differentiating participants across the AD clinical spectrum (Table 2; Fig. 2).



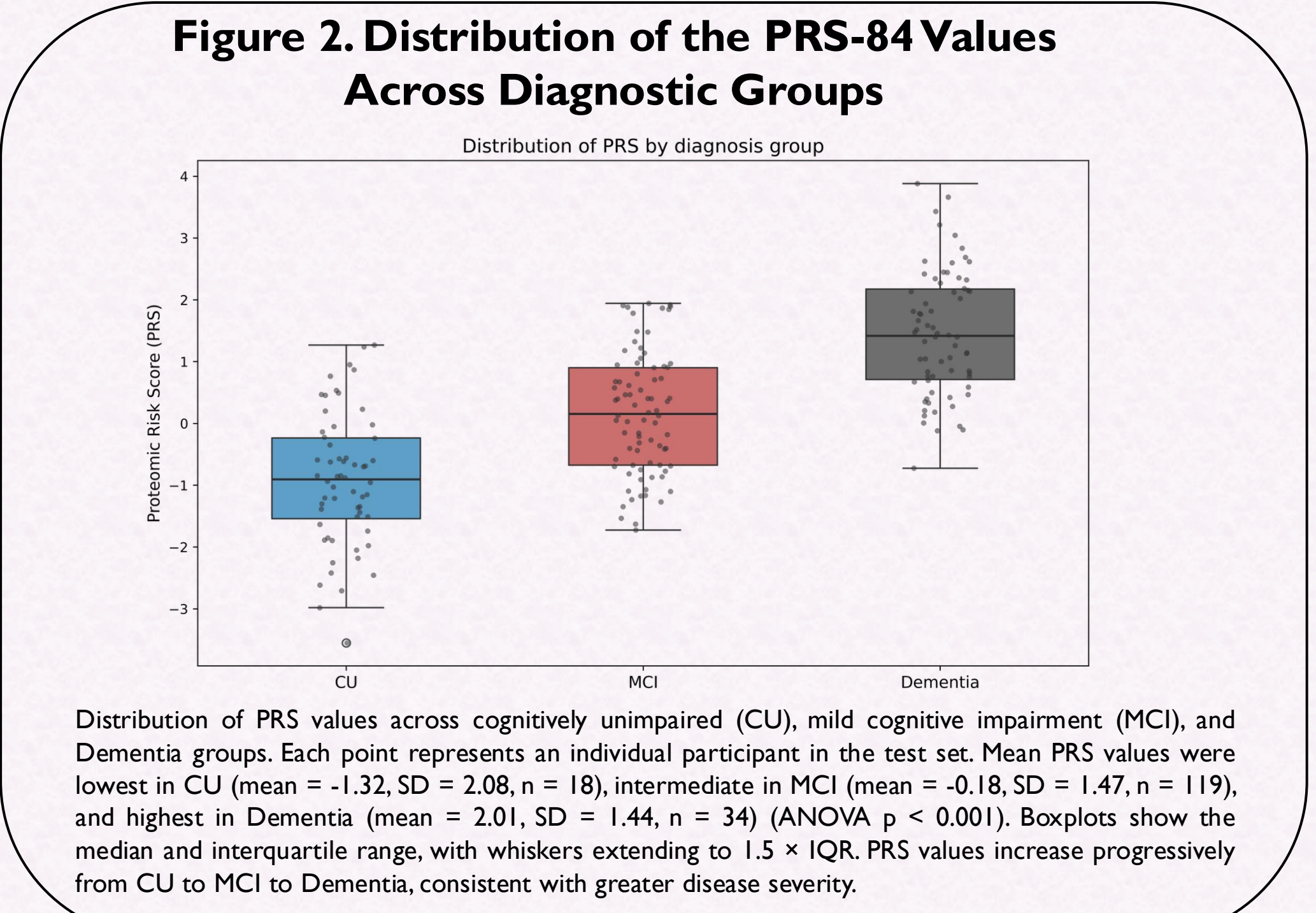
The proteins comprising the proteomic risk score (PRS-84) formed a highly interconnected biological network (protein-protein interaction enrichment $p < 1.0 \times 10^{-16}$).

Proteins	β weights
Pregnancy-Associated Plasma Protein A (PAPPA)	0.47
Vitronectin (VTN)	0.42
Alpha-1-Microglobulin (AMBIP)	-0.42
Peptide YY (PYY)	-0.38
Alpha-2-Macroglobulin (A2M)	-0.37
Brain Natriuretic Peptide (NPPB)	-0.36
Apolipoprotein B (APOB)	-0.34
Aspartate Aminotransferase / Serum Glutamic-Oxaloacetic Transaminase (AST)	0.34
Chromogranin A (CHGA)	0.32
Cortisol (NR3C1)	-0.31
Immunoglobulin M (IGHM)	0.29
Apolipoprotein A-II (APOA2)	0.29
C-Reactive Protein (CRP)	0.28
Heart-Type Fatty Acid Binding Protein (FABP3)	0.27
Placenta Growth Factor (PGF)	0.27
Intercellular Adhesion Molecule 1 (ICAM1)	-0.24
Tenascin-C (TNC)	-0.23
Apolipoprotein C-III (APOC3)	0.22
Interleukin-6 Receptor (IL6R)	0.22
Uromodulin / Tamm-Horsfall Protein (UMOD)	0.21

Table 2. Diagnostic Performance of the PRS-84				
Clinical Contrast	Sample Size (n)	AUC	95% Confidence Interval	P value
Mild Cognitive Impairment vs Cognitive Unimpaired	137	0.68	0.51 – 0.84	0.033
Dementia vs Cognitive Unimpaired	52	0.90	0.80 – 0.99	<0.001
Dementia vs Mild Cognitive Impairment	153	0.86	0.78 – 0.93	<0.001

AUC, area under the receiver operating characteristic curve.

Higher PRS-84 was associated with poorer cognition, greater functional impairment, worse verbal memory, lower CSF Aβ42, and higher CSF p-tau181 and t-tau (Table 3).



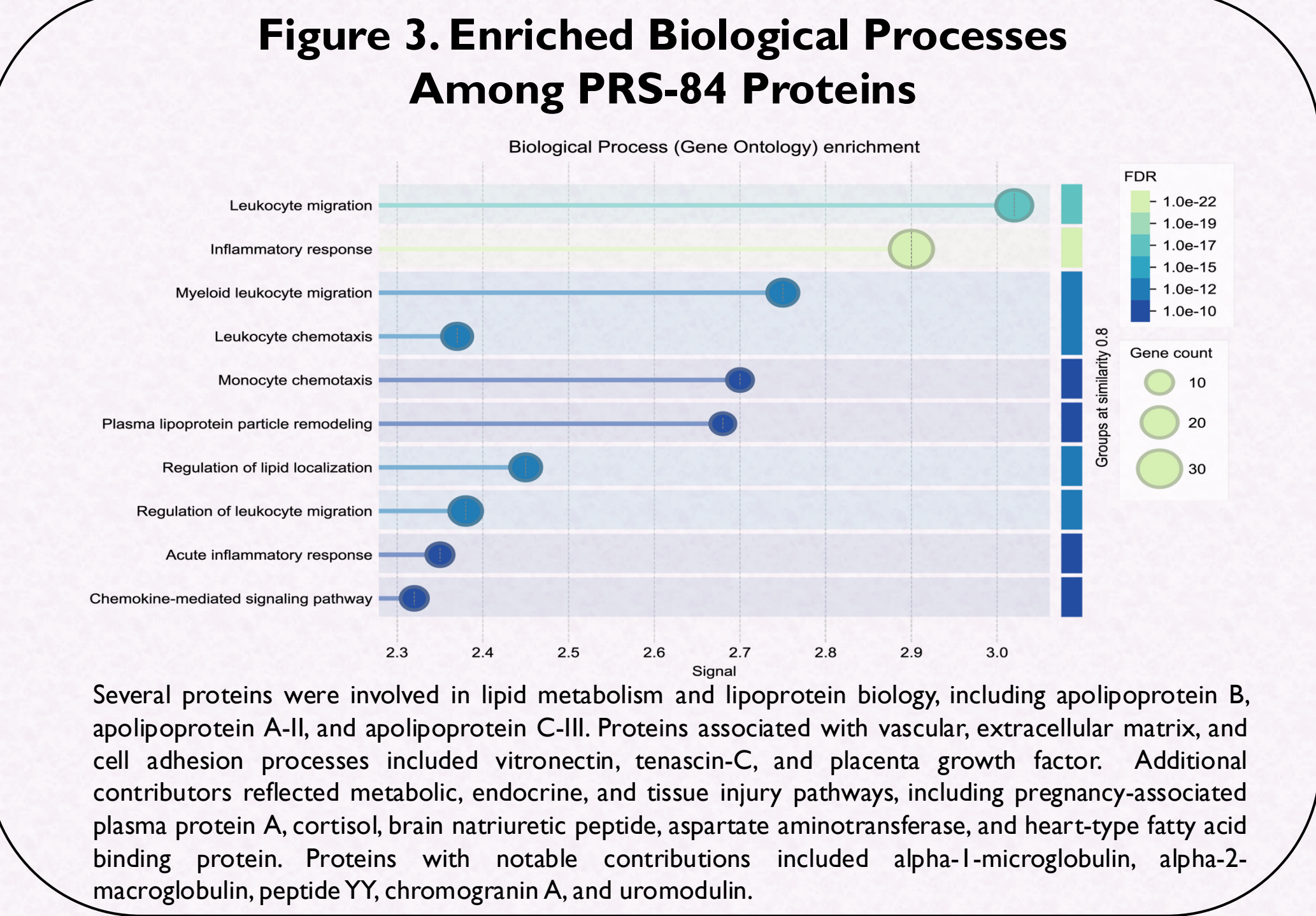
Distribution of PRS values across cognitively unimpaired (CU), mild cognitive impairment (MCI), and Dementia groups. Each point represents an individual participant in the test set. Mean PRS values were lowest in CU (mean = -1.32, SD = 2.08, n = 18), intermediate in MCI (mean = -0.18, SD = 1.47, n = 119), and highest in Dementia (mean = 2.01, SD = 1.44, n = 34) (ANOVA $p < 0.001$). Boxplots show the median and interquartile range, with whiskers extending to $1.5 \times$ IQR. PRS values increase progressively from CU to MCI to Dementia, consistent with greater disease severity.

Table3. Associations Between PRS-84, Cognitive Outcomes and CSF Biomarkers						
Variables	n	β coefficient	SE	Statistic	p value	q value
MMSE Total	171	-0.54	0.09	-6.12	< 0.001	< 0.001
CDR Global	171	0.04	0.01	4.21	< 0.001	< 0.001
ADAS Cog I I	171	0.91	0.25	3.66	< 0.001	< 0.001
ADAS Cog I 3	169	1.31	0.36	3.64	< 0.001	< 0.001
RAVLT Immediate	171	-1.26	0.39	-3.19	0.002	0.003
CDRSB	171	0.36	0.06	6.31	< 0.001	< 0.001
RAVLT Learn	171	-0.30	0.09	-2.98	0.003	0.005
DIGIT Span	170	-1.39	0.48	-2.86	0.005	0.006
TRAILS B	168	10.45	3.54	2.95	0.004	0.005
TRAILS A	171	3.52	1.27	2.76	0.006	0.007
CLOCK Draw	171	-0.18	0.04	-4.13	< 0.001	< 0.001
CSF Aβ-42	98	-0.09	0.02	-3.87	< 0.001	0.002
CSF p-tau181	98	0.07	0.02	3.48	< 0.001	0.004
CSF t-tau	98	0.06	0.02	3.24	0.002	0.005

Notes: Models adjusted for age, sex, body mass index (BMI), years of education, and APOE ε4 status. p values represent two-sided tests from linear regression models, and q values correspond to false discovery rate (FDR)-adjusted p values using the Benjamini-Hochberg procedure.

Abbreviations: ADAS-Cog = Alzheimer’s Disease Assessment Scale–Cognitive Subscale; Aβ = amyloid-β; CDR Global = Clinical Dementia Rating Global Score; CDRSB = Clinical Dementia Rating Sum of Boxes; CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination; p-tau = phosphorylated tau; RAVLT = Rey Auditory Verbal Learning Test; SE = Standard Error; t-tau = total tau; Trails A and B = Trail Making Test Parts A and B.

PRS-84 proteins are clustered within coherent biological pathways (Figure 3).



Several proteins were involved in lipid metabolism and lipoprotein biology, including apolipoprotein B, apolipoprotein A-II, and apolipoprotein C-III. Proteins associated with vascular, extracellular matrix, and cell adhesion processes included vitronectin, tenascin-C, and placenta growth factor. Additional contributors reflected metabolic, endocrine, and tissue injury pathways, including pregnancy-associated plasma protein A, cortisol, brain natriuretic peptide, aspartate aminotransferase, and heart-type fatty acid binding protein. Proteins with notable contributions included alpha-1-microglobulin, alpha-2-macroglobulin, peptide YY, chromogranin A, and uromodulin.

Results (continued)

Sensitivity Analyses

- Across diagnostic classification, PRS-pathway-restricted models showed lower discrimination than PRS-84 (Figures 4-6).
- Results suggest that PRS-84 captures broader biological information.
- The integrated multi-protein architecture of PRS-84 outperforms individual pathway subsets.

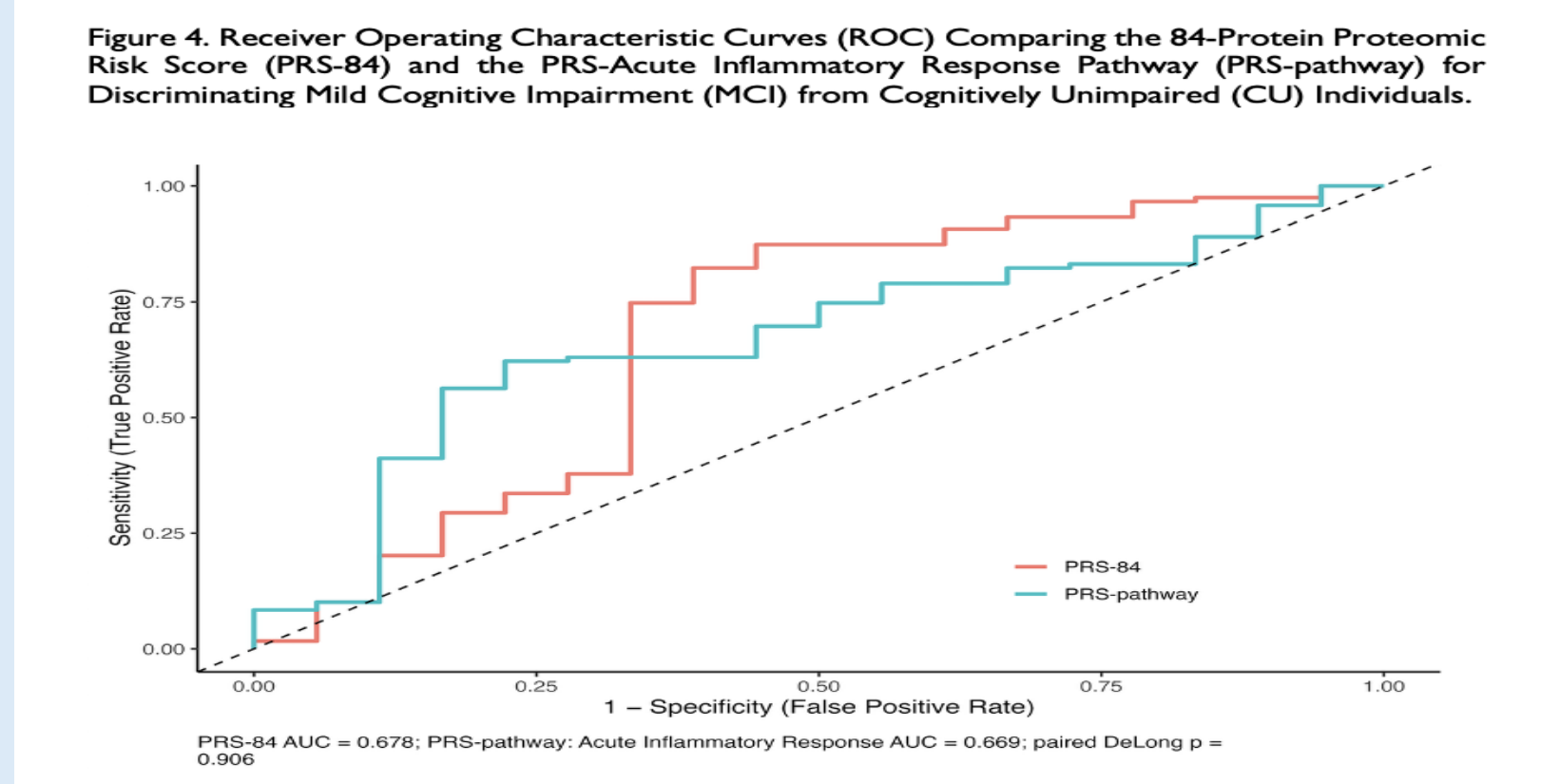


Figure 4. Receiver Operating Characteristic Curves (ROC) Comparing the 84-Protein Proteomic Risk Score (PRS-84) and the PRS-Acute Inflammatory Response Pathway (PRS-pathway) for Discriminating Mild Cognitive Impairment (MCI) from Cognitively Unimpaired (CU) Individuals.

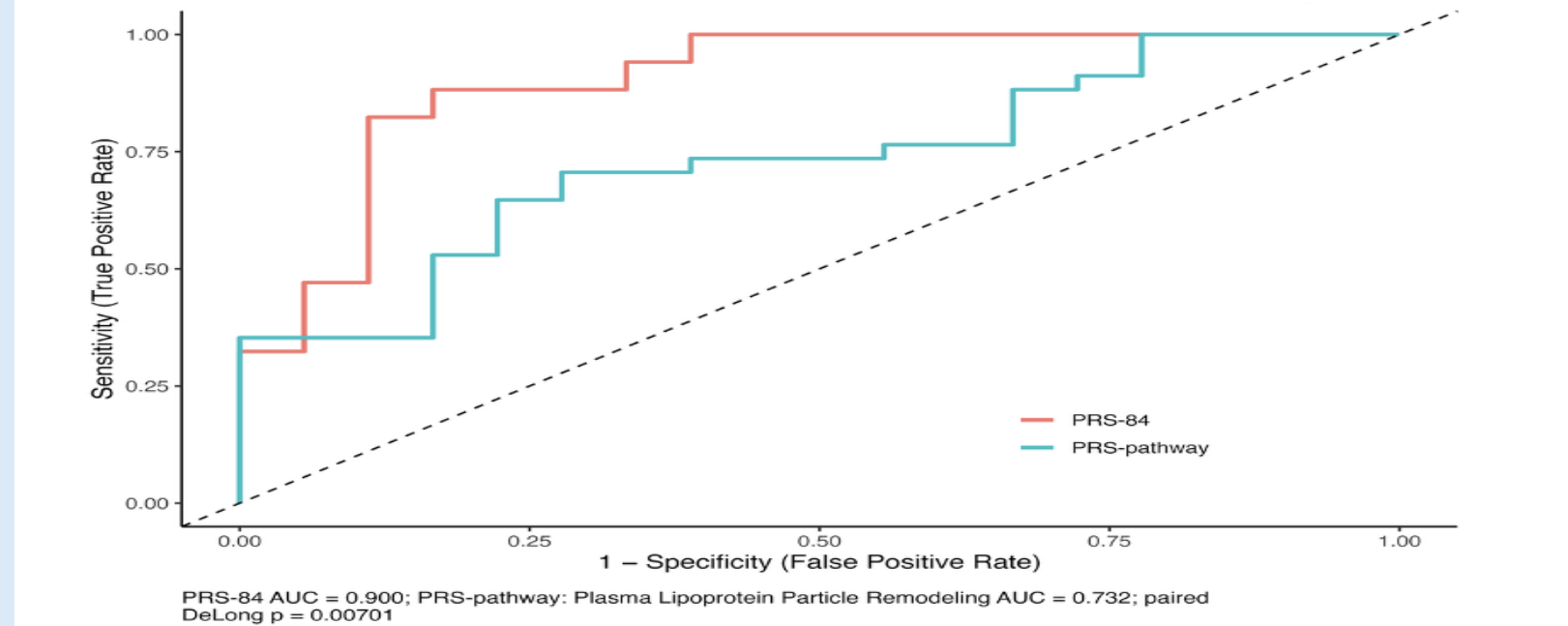
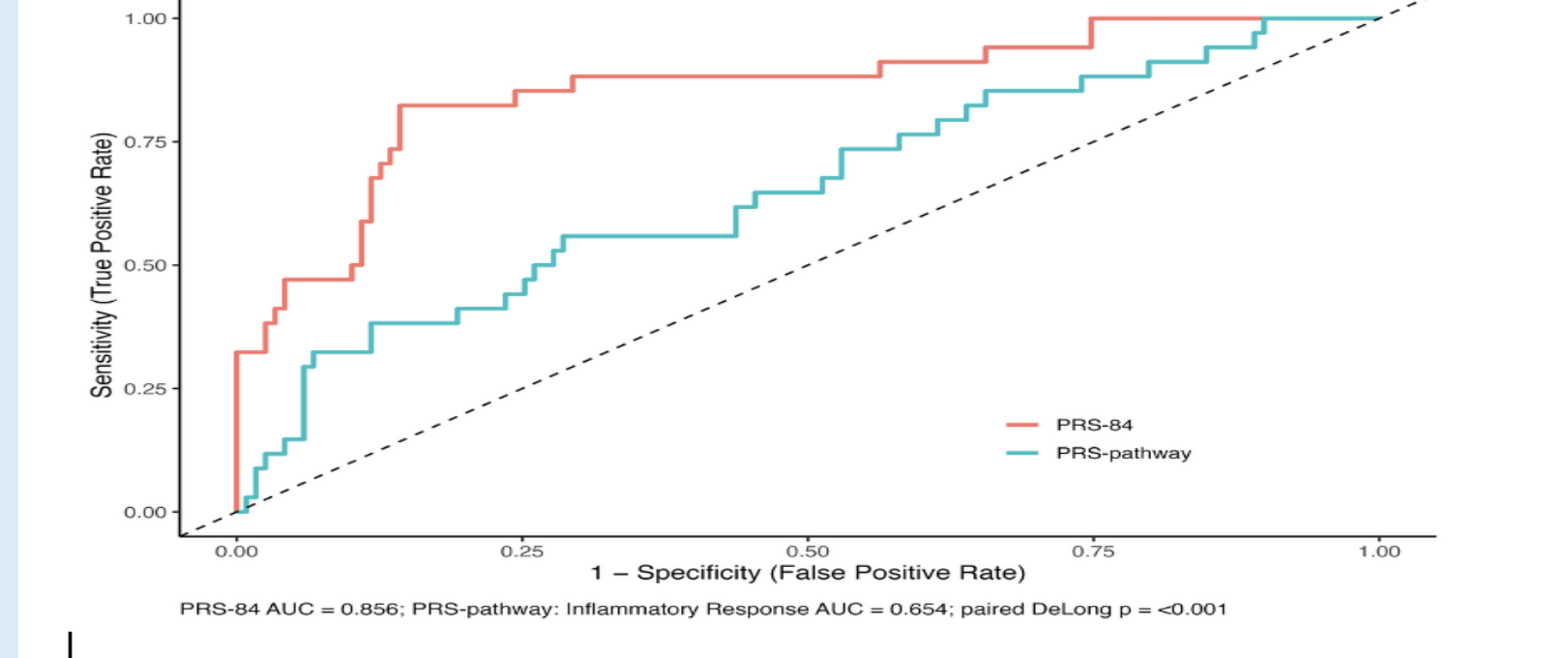


Figure 5. Receiver Operating Characteristic Curves (ROC) Comparing the 84-Protein Proteomic Risk Score (PRS-84) and the PRS-Plasma Lipoprotein Particle Remodeling Pathway (PRS-pathway) for Discriminating Dementia from Cognitively Unimpaired (CU) Individuals.



- Overall, PRS-84 performance was consistent across sex and APOE4 carriers/non-carriers (Table 4), supporting the robustness and generalizability of the proteomic risk score.

Table 4. Sex-stratified discriminatory performance of the proteomic risk score across diagnostic contrasts.					
Sex	Contrast	n	AUC	95% CI	p value
Female	Dementia vs CU	23	0.94	0.86–1.00	< 0.001
Female	MCI vs CU	55	0.68	0.48–0.88	0.08
Female	Dementia vs MCI	60	0.79	0.65–0.93	< 0.001
Male	Dementia vs CU	29	0.87	0.72–1.00	< 0.001
Male	MCI vs CU	82	0.67	0.41–0.94	< 0.001
Male	Dementia vs MCI	93	0.89	0.80–0.99	< 0.001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CU = cognitively unimpaired; MCI = mild cognitive impairment.

Table 5. *APOE4*: stratified discriminatory performance of the proteomic risk score across diagnostic contrasts.

<i>APOE4</i> presence	Contrast	n	AUC	95% CI	p value
No	Dementia vs CU	26	0.88	0.74–1.00	< 0.001
No	MCI vs CU	75	0.67	0.49–0.85	0.006
No	Dementia vs MCI	67	0.85	0.70–0.99	< 0.001
Yes	Dementia vs CU	26	1.00	NA	NA
Yes	MCI vs CU	62	0.90	NA	NA
Yes	Dementia vs MCI	86	0.86	0.77–0.95	< 0.001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CU = cognitively unimpaired; MCI = mild cognitive impairment; *APOE4* = apolipoprotein E ε4 allele.

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CU = cognitively unimpaired; MCI = mild cognitive impairment.

Table 5. APOE4 stratified discriminatory performance of the proteomic risk score across diagnostic contrasts.					
APOE4 presence	Contrast	n	AUC	95% CI	p value
No	Dementia vs CU	26	0.88	0.74–1.00	< 0.001
	MCI vs CU	75	0.67	0.49–0.85	0.006
No	Dementia vs MCI	67	0.85	0.70–0.99	< 0.001
	Dementia vs CU	26	1.00	NA	NA
Yes	MCI vs CU	62	0.90	NA	NA
	Dementia vs MCI	86	0.86	0.77–0.95	< 0.001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CU = cognitively unimpaired; MCI = mild cognitive impairment; APOE4 = apolipoprotein E ε4 allele.

Conclusion

- A plasma protein-derived PRS (PRS-84) captures an immune-metabolic AD signature linked to diagnosis, cognition and CSF AD-relevant biomarkers, warranting validation.