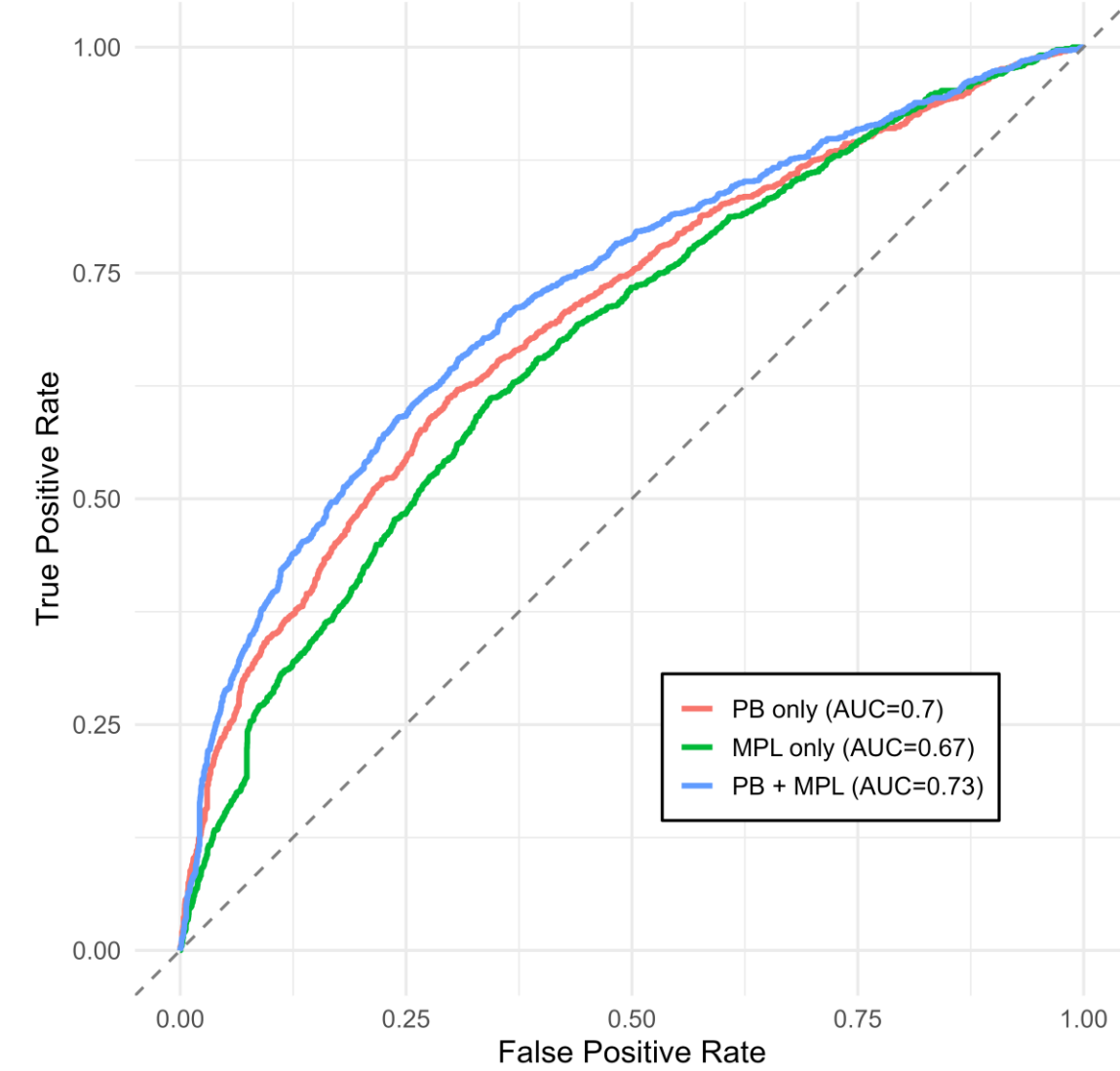
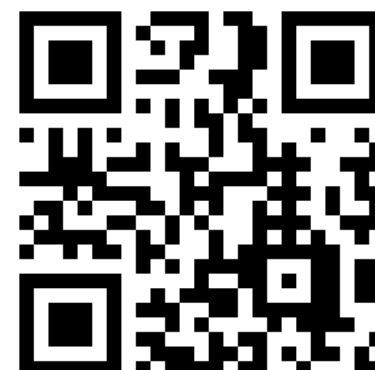


Enhanced Detection of Cognitive Impairment via Multimodal ML Using Plasma Biomarkers & Metabolic_Psychosocial_Lifestyle Factors

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- 1) Multimodal SVM outperformed biomarker-only and Metabolic_Psychosocial_Lifestyle-only models for cognitive impairment detection.
2) The combined model achieved the best performance (AUC = 0.73, NPV = 85.78%).
3) Integrating biological and Metabolic_Psychosocial_Lifestyle factors improves Alzheimer's disease diagnosis.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																												
Accurate identification of cognitive impairment remains challenging when relying on biological markers alone. Multimodal machine-learning approaches that integrate plasma biomarkers with metabolic, psychosocial, and lifestyle factors may better capture the mechanisms underlying cognitive impairment. We hypothesized that AD diagnostic accuracy would improve when plasma-based neurodegenerative biomarkers are jointly modeled with Metabolic, Psychosocial, and Lifestyle factors, including body mass index (BMI), social support, chronic stress, and exercise, compared with biomarker-only or Metabolic_Psychosocial_Lifestyle models. This hypothesis is motivated by the complementary roles of plasma biomarkers in indexing neuropathology, BMI in reflecting metabolic and inflammatory processes, psychosocial factors in modulating hypothalamic–pituitary–adrenal axis activity and neuroinflammation, and exercise in supporting neurovascular and neurotrophic resilience.	We used cognitively normal participants from the Health & Aging Brain Study – Health Disparities (HABS-HD),[1] a richly phenotyped multimodal dataset designed for Alzheimer’s disease research. A total of 4,569 observations were included (3,214 from visit 1, 1,158 from visit 2, and 197 from visit 3), comprising 1,124 cognitively impaired (CI; AD and MCI) and 3,445 cognitively unimpaired (CU) participants. Support vector machine (SVM) classifiers were trained to discriminate CI from CU using three feature sets: (1) plasma biomarkers only, (2) Metabolic_Psychosocial_Lifestyle factors only (BMI, social support, chronic stress, and exercise), and (3) a combined multimodal feature set integrating both domains. Model hyperparameters were optimized using 10-times repeated five-fold cross-validation.[2,3]	<table><tr><th></th><th>PB only</th><th>MPL only</th><th>PB + MPL</th></tr><tr><td>PPV</td><td>39.38%</td><td>35.56%</td><td>41.21%</td></tr><tr><td>ACC</td><td>67.15%</td><td>62.81%</td><td>68.64%</td></tr><tr><td>SN</td><td>62.19%</td><td>62.99%</td><td>64.41%</td></tr><tr><td>SP</td><td>68.77%</td><td>62.76%</td><td>70.01%</td></tr><tr><td>NPV</td><td>84.79%</td><td>83.86%</td><td>85.78%</td></tr><tr><td>AUC</td><td>70.14%</td><td>67.18%</td><td>72.77%</td></tr></table> The plasma biomarker-only model achieved moderate discrimination, with an AUC of 0.70, sensitivity of 62.19%, specificity of 68.77%, and NPV of 84.79%. The Metabolic_Psychosocial_Lifestyle-only model showed lower performance (AUC = 0.67, sensitivity = 62.99%, specificity = 62.76%, NPV = 83.86%). In contrast, the combined plasma biomarker + Metabolic_Psychosocial_Lifestyle model demonstrated the best performance, yielding a higher AUC (0.73), improved sensitivity (64.41%) and specificity (70.01%), and the highest NPV (85.78%).		PB only	MPL only	PB + MPL	PPV	39.38%	35.56%	41.21%	ACC	67.15%	62.81%	68.64%	SN	62.19%	62.99%	64.41%	SP	68.77%	62.76%	70.01%	NPV	84.79%	83.86%	85.78%	AUC	70.14%	67.18%	72.77%	 Integrating plasma biomarkers with Metabolic_Psychosocial_Lifestyle factors improves discrimination of cognitively impaired individuals from cognitively unimpaired participants. These findings support the value of multimodal machine-learning models for AD diagnosis and highlight the complementary contributions of biological pathology and metabolic, psychosocial, and lifestyle context.	[1] O'Bryant SE, Petersen M, Hall J, Johnson L, Team H-HS (2022) Metabolic Factors Are Related to Brain Amyloid Among Mexican Americans: A HABS-HD Study. J Alzheimers Dis 86, 1745-1750. [2] Zhang F, Petersen M, Johnson L, Hall J, O'Bryant SE, Health, Aging Brain Study Study T (2023) Comorbidities Incorporated to Improve Prediction for Prevalent Mild Cognitive Impairment and Alzheimer's Disease in the HABS-HD Study. J Alzheimers Dis 96, 1529-1546. [3] Zhang F, Petersen M, Johnson L, Hall J, O'Bryant SE (2021) Recursive Support Vector Machine Biomarker Selection for Alzheimer's Disease. J Alzheimers Dis 79, 1691-1700.
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