

Non-Invasive Multi-Spectral Fundus Images Accurately Detect Cognitive Impairment in Alzheimer’s Disease

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Multi-spectral fundus images has promising potential as a digital biomarker for sensitively detecting cognitive impairment in AD

INTRODUCTION & METHODS

RESULTS

CONCLUSION

The utility of multi-spectral fundus imaging in identifying cognitive abnormalities in Alzheimer’s disease in remains to be fully elucidated.

We analyzed data from 178 participants in the Greater Bay Area Healthy Aging Brain Study, comprising 137 cognitively unimpaired (CU) and 41 cognitively impaired (CI) individuals. All participants underwent cognitive assessments, plasma sample collection, and multi-spectral fundus imaging. Phosphorylated tau217 (p-Tau217), plasma β -amyloid42/ β -amyloid40 (A β 42/40), p-Tau217/A β 42, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) were measured using the Lumipulse/Simoa platform.

Multi-spectral imaging (MSI) indices were derived from fundus images obtained at 548nm and 605nm wavelengths. A composite Fundus Panel score was generated by integrating all MSI indices using a random forest algorithm, which also incorporates age, sex, and education. General linear models were used to examine the correlations between fundus-derived indicators and well-established AD biomarkers. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC).

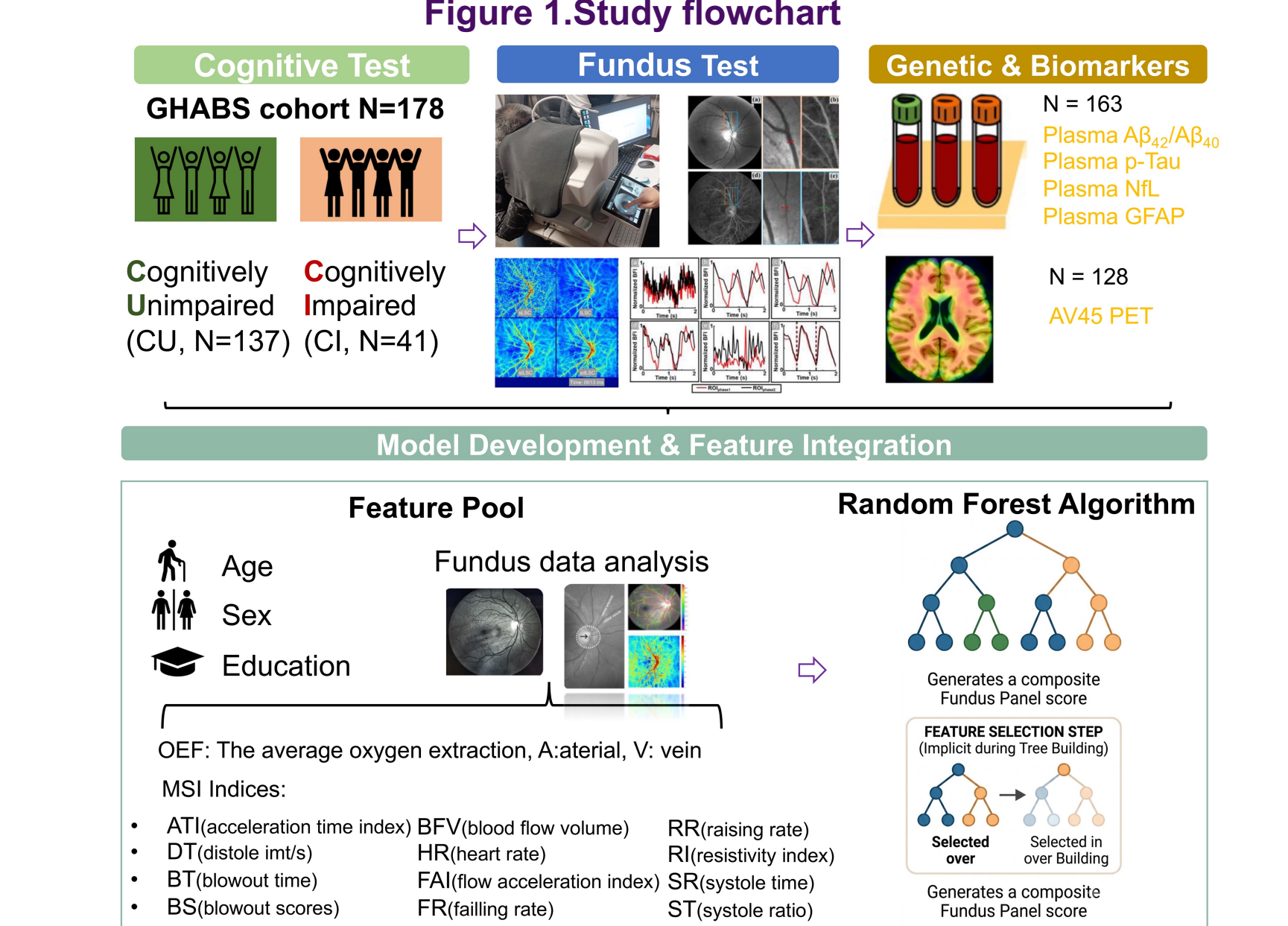
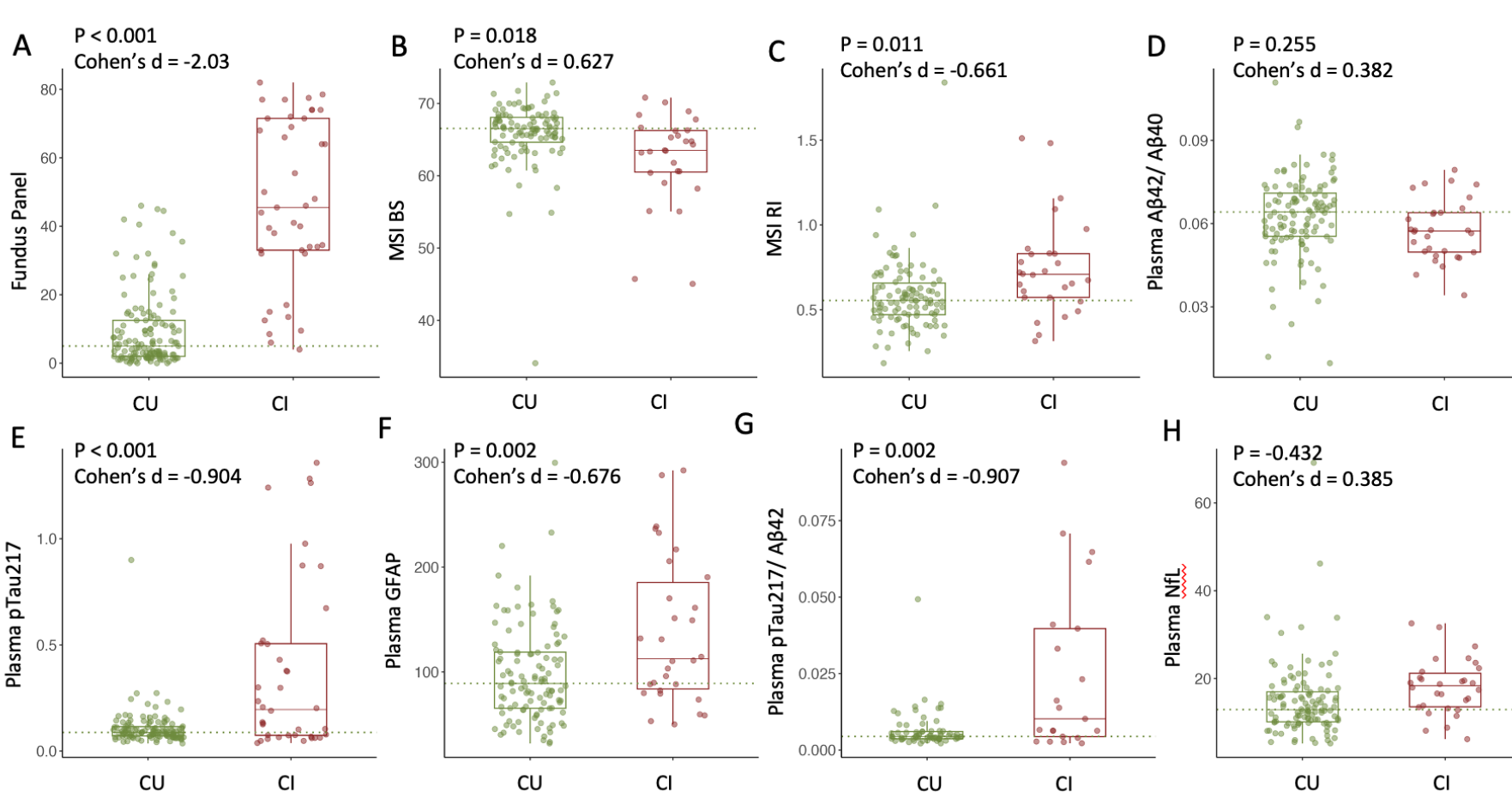


Table 1. Demographic characteristics

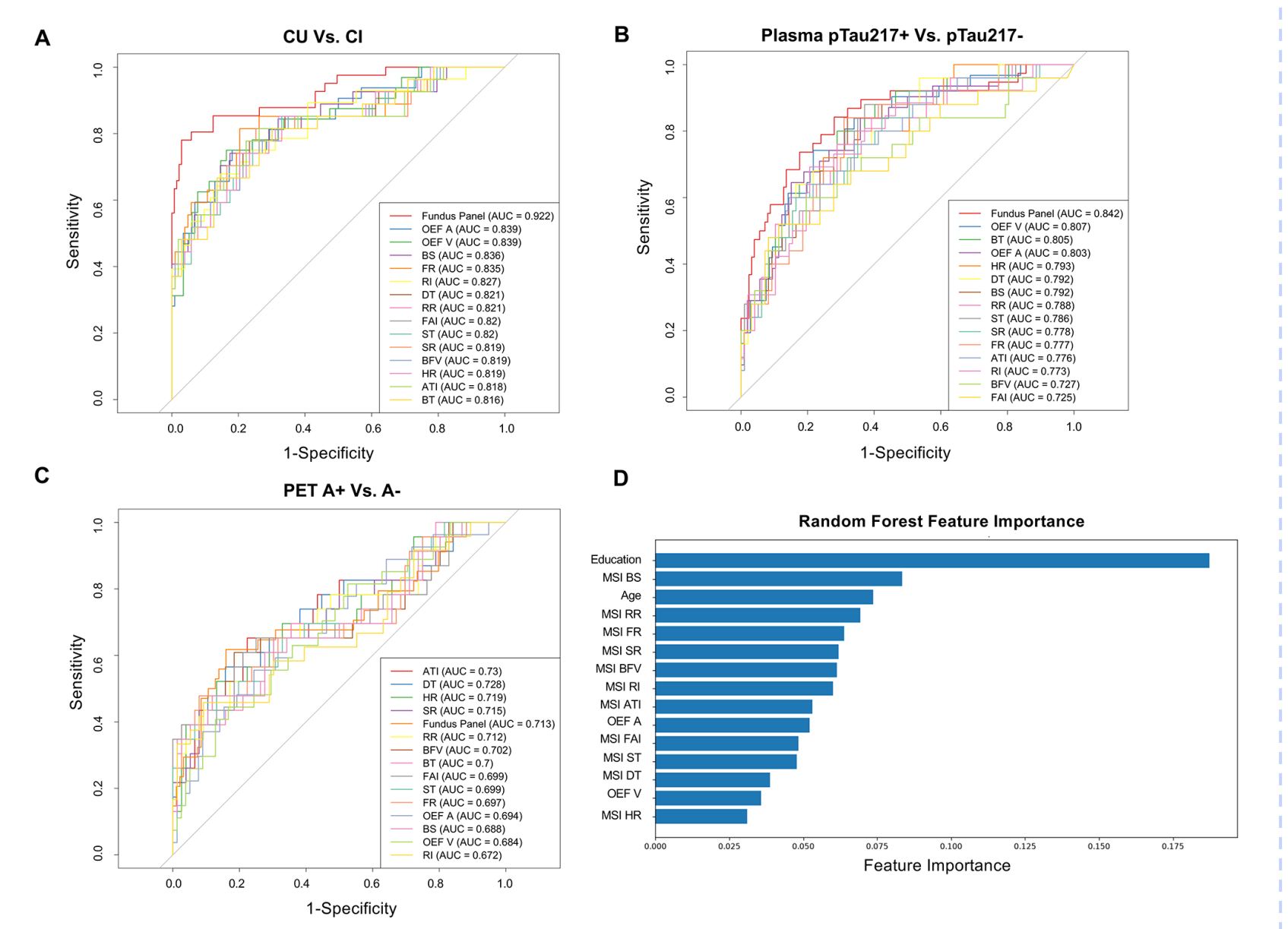
	CU	CI	Overall
	(N=137)	(N=41)	(N=178)
Age, mean(SD)	63.6 (7.05)	69.2 (6.98)	64.9 (7.41)
Education, years, mean(SD)	14.2 (2.58)	10.3 (3.56)	13.3 (3.26)
Sex, n (%)			
Female	88 (64.2%)	26 (63.4%)	114 (64.0%)
Male	49 (35.8%)	15 (36.6%)	64 (36.0%)
MoCA scores, mean(SD)	27.3 (2.00)	17.5 (6.89)	25.1 (5.58)
APOE- ϵ 4 carriers, n (%)	47 (34.3%)	20 (48.8%)	67 (37.6%)
Plasma pTau217 concentration	0.116 (0.0976)	0.386 (0.421)	0.185 (0.256)
Missing	41 (29.9%)	8 (19.5%)	49 (27.5%)
A β PET status			
A-	83 (60.6%)	11 (26.8%)	94 (52.8%)
A+	12 (8.8%)	22 (53.7%)	34 (19.1%)
Missing	42 (30.7%)	8 (19.5%)	50 (28.1%)

Figure 2. Comparisons of fundus indicators and plasma biomarkers between cognitively unimpaired and impaired group



Compared with the CI group, CU individuals showed lower Fundus Panel scores (β = 27.45; 95% CI, 1.008 to 1.517), and RI (β = 0.13; 95% CI, 0.136 to 1.040), and lower BS (β = -2.84; 95% CI, -1.025 to -0.095). The between-group discriminative ability of the Fundus Panel surpassed that of plasma p-Tau217, A β 42/40, p-Tau217/A β 42 ratio, GFAP, and NfL.

Figure 3. Receiver operating characteristic curves analysis of MSI index and Fundus Panel performance in classifying clinical and pathological stages



The Fundus Panel scores and MSI indices indicated outstanding classification performance (AUC: 0.922) in distinguishing clinically impaired individuals from unimpaired counterparts, and showed good discriminatory ability in screening for plasma pTau217 positivity. Additionally, acceptable accuracy was observed for differentiating brain amyloid status.

REFERENCE

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[2] Salajková, Z., Ciasca, G., Di Lorenzo, F. *et al*. Non-invasive screening of alzheimer’s disease via label-free tri-spectral retinal imaging. *Sci Rep* **16**, 5083 (2026). <https://doi.org/10.1038/s41598-026-35383-y>.

Fundus image–derived OEF, BS, FR, and RI indicators were found to be effective in detecting cognitive decline in older adults and performed well in identifying abnormal plasma pTau217 concentrations. The composite Fundus Panel risk scores outperformed current plasma biomarkers in distinguishing cognitively impaired patients from cognitively unimpaired individuals, highlighting the promising potential of fundus panel risk scores as digital biomarkers for early, large-scale screening of cognitive impairment in populations at risk for Alzheimer's disease.

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