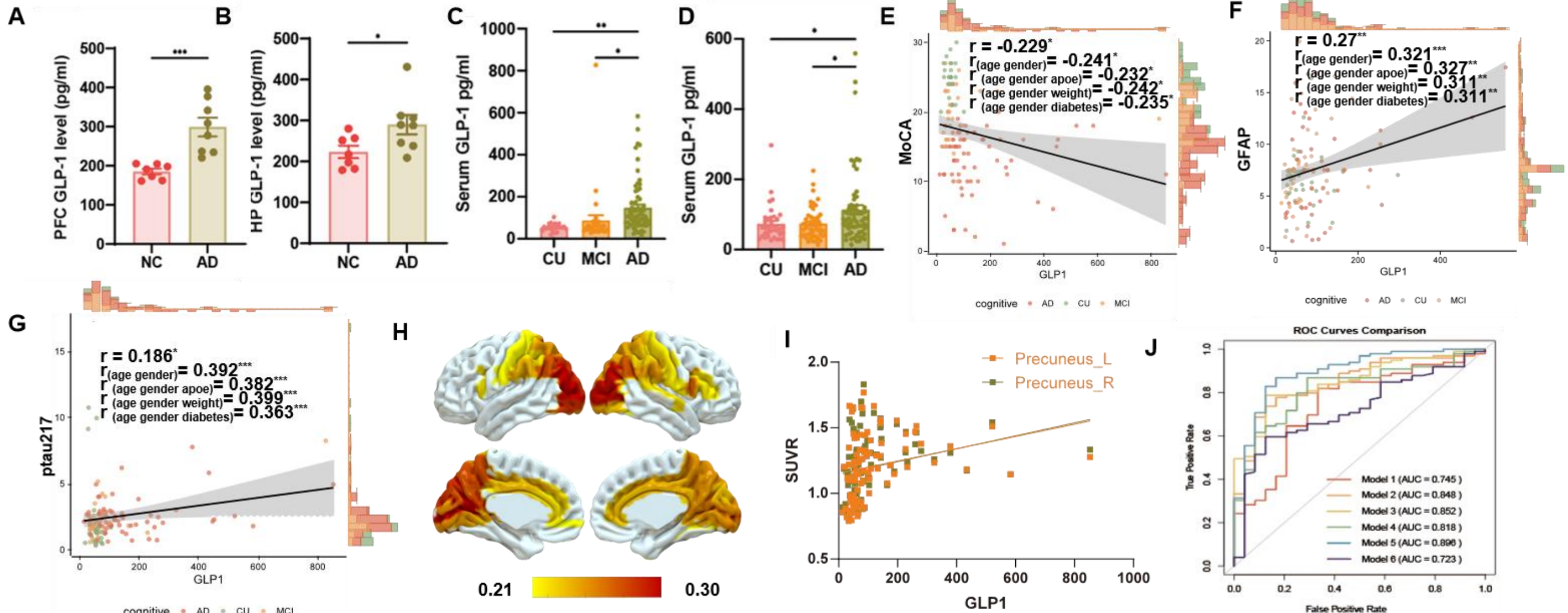


Endogenous GLP-1 as a Novel Alzheimer's Disease Biomarker Associated with Neuroinflammation and Aβ Pathology



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BACKGROUND	METHODS	RESULTS	CONCLUSIONS
Alzheimer’s disease (AD) is characterized by amyloid-β deposition, tau pathology, neurodegeneration , and sustained neuroinflammation. Although GLP-1 receptor agonists show neuroprotective effects in preclinical AD models, clinical outcomes remain inconsistent. The role of endogenous GLP-1 across the AD continuum remains unclear. This study investigated whether serum GLP-1 reflects AD related pathological burden and clinical disease severity.	Two independent clinical cohorts were included: the Renji cohort (n = 123) and SheMountain cohort (n = 127) , comprising cognitively unimpaired individuals, patients with mild cognitive impairment , and AD dementia. Serum GLP-1 , GFAP, Aβ40, Aβ42, and pTau217 were quantified, together with APOE genotyping , neuropsychological assessment , structural MRI, and Aβ PET imaging. Post-mortem GLP-1 levels were examined in the prefrontal cortex and hippocampus . Partial correlation , mediation analysis , and machine-learning models were used to evaluate pathological associations and diagnostic performance.	Endogenous GLP-1 was significantly elevated in both serum and post-mortem brain tissue from AD patients. Serum GLP-1 increased progressively across the cognitive continuum from cognitively unimpaired individuals to MCI and AD dementia. Higher GLP-1 levels were associated with worse cognitive performance, increased GFAP, elevated pTau217, greater Aβ PET burden, and regional cortical thinning. Exploratory mediation analysis suggested that GLP-1 and GFAP were statistically positioned along the association between amyloid burden and tau pathology. A multimarker model integrating GLP-1 with pTau217, GFAP, Aβ42, APOE status, age, and gender achieved strong diagnostic performance for cognitive impairment, showing robust predictive accuracy. 	Elevated endogenous GLP-1 in AD may represent a reactive but insufficient compensatory response to pathological stress. Serum GLP-1 may serve as a non-core, inflammation-metabolism-related blood biomarker that reflects multidimensional AD burden, including neuroinflammation, amyloid deposition, tau pathology, brain atrophy, and cognitive decline. 