



Plasma Biomarker–specific, Non-linear Associations Of Amyloid PET Burden In Early-onset Alzheimer’s Disease

Bora Yoon¹, Dong Won Yang¹, Hyuk-je Lee¹, Eun-Joo Kim², Na-Yeon Jung³, So Young Moon⁴, Sun Min Lee⁴, Hee Jin Kim⁵, Hyemin Jang⁶ and LEAF investigators

¹Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, ²Department of Neurology, Pusan National University Hospital, Busan, Republic of Korea

³Neurology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, ⁴Neurology, Ajou University School of Medicine, Suwon, Republic of Korea,

⁵Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ⁶Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

INTRODUCTION

Background

EOAD (onset <65 yrs) shows substantial heterogeneity at CDR 0.5, spanning prodromal MCI to very mild dementia, yet global amyloid burden is comparable — consistent with amyloid saturation. Plasma biomarkers (p-tau181, p-tau217, GFAP, NfL) reflect distinct pathophysiological processes but their non-linear coupling with amyloid PET across clinical severity was unexplored.

Objectives

- ① Characterize amyloid PET – plasma biomarker associations at CDR 0.5
- ② Assess plasma biomarker – clinical severity (CDR-SB) associations
- ③ Estimate non-linear marginal effects of amyloid burden on plasma biomarkers across CDR-SB spectrum using restricted cubic spline (RCS) models

RESULTS

Although global amyloid burden was comparable between EOMCI and EOAD-0.5 (93.77 vs. 93.33 Centiloid, p=0.990), plasma GFAP, p-tau217, and p-tau181 concentrations were significantly higher in EOAD-0.5 (Table 2; Figure 1). Associations between plasma biomarkers and clinical severity differed by stage: positive associations with CDR-SB were observed in EOMCI, whereas these associations were attenuated or reversed in EOAD-0.5 (Figure 2). RCS modeling revealed biomarker-specific patterns of amyloid–plasma coupling across the CDR-SB spectrum, with sustained positive coupling for p-tau181 and early attenuation of GFAP coupling (Table 3; Figure 3).

CONCLUSION

Despite comparable global amyloid burden between EOMCI and EOAD-0.5 (93.8 vs. 93.3 CL, p=0.990), consistent with amyloid saturation, plasma p-tau181, p-tau217, and GFAP were significantly higher in EOAD-0.5, indicating downstream pathological divergence. RCS modeling revealed biomarker-specific non-linear coupling with amyloid burden across the CDR-SB spectrum: p-tau181 showed the most sustained association with no zero-crossing (significant at CDR-SB 0.5, 1.0, and 1.5), whereas GFAP coupling attenuated and crossed zero at CDR-SB 2.11 (significant at 0.5 and 1.0), while NfL and p-tau217 showed no significant effects. These findings, not captured by conventional linear models, support biomarker-specific interpretation across severity levels within a uniform CDR 0.5 stage.

Table 1. Participant Characteristics				
Characteristic	Total	EOMCI	EOAD-0.5	p
Age (years)	61.1±5.7	62.5±5.0	60.0±6.1	0.099
Sex, female	65 (62.5%)	26 (56.5%)	39 (67.2%)	0.310
Education (yr)	12.3±3.8	13.4±4.0	11.4±3.5	0.007*
MMSE ^a	23.6±3.2	25.3±2.7	21.9±2.7	<0.001*
CDR-SB	2.59±1.22	1.63±1.00	3.34±0.75	<0.001*
APOE ε4(+)	53 (51%)	27 (58.7%)	26 (44.8%)	0.173

^aKorean MMSE n=53. *p<0.05. Means±SD or n(%).

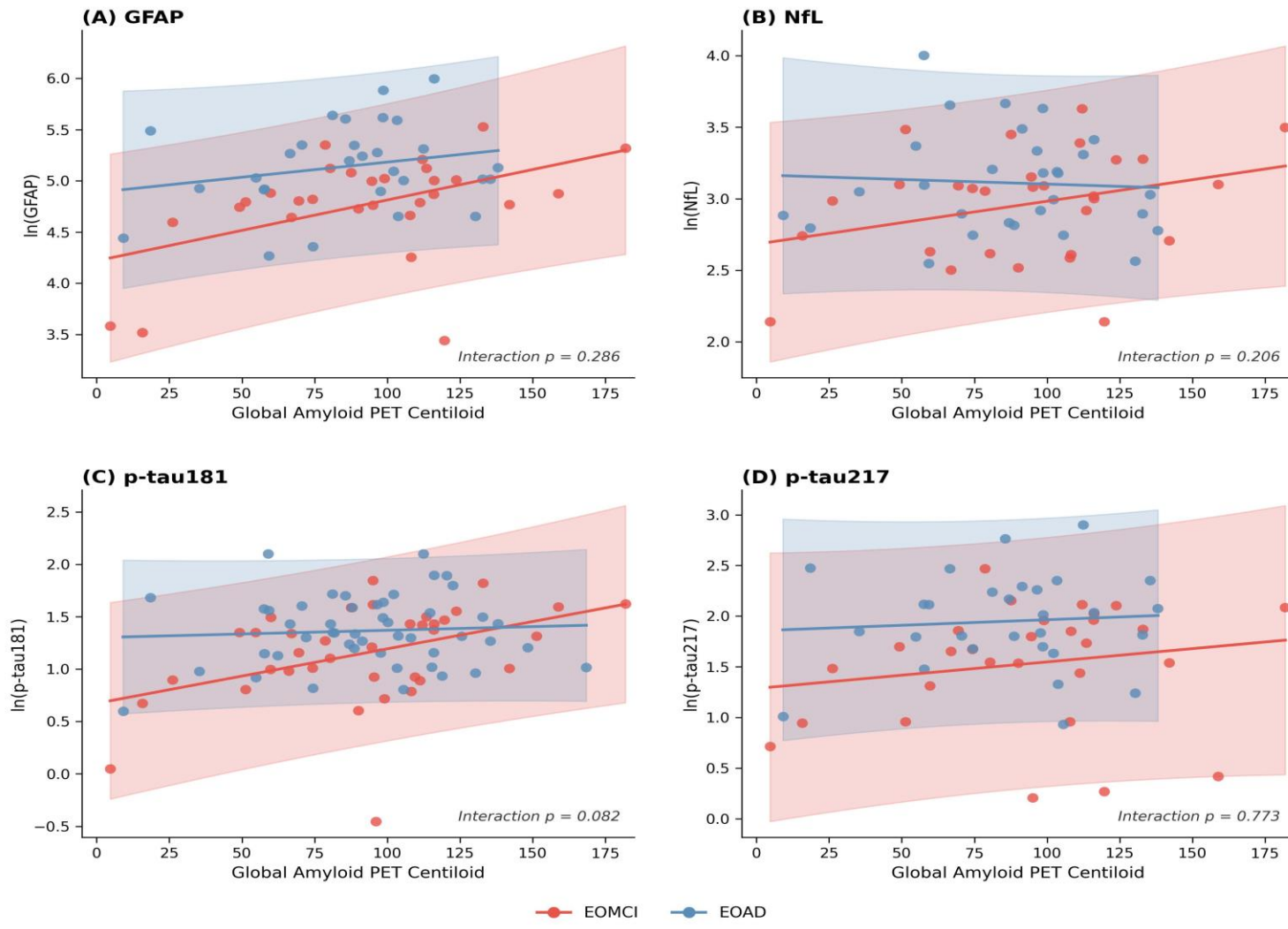
Table 2. Amyloid PET & Plasma Biomarkers by Group			
Biomarker	EOMCI	EOAD-0.5	p
Global CL (n=86)	93.77±38.78	93.33±31.94	0.990
NfL (pg/mL)	21.3±7.9	25.6±10.5	0.124
GFAP (pg/mL)	137.9±54.0	189.3±76.2	0.003*
p-tau217 (pg/mL)	6.06±3.53	8.26±3.64	0.004*
p-tau181 (pg/mL)	3.54±1.24	4.23±1.48	0.031*
Aβ40/42 ratio	17.5±3.5	17.6±3.6	0.740

n=72–73 (Swedish Simoa); p-tau181: in-house Simoa n=103. *p<0.05.

Table 3. RCS Marginal Effects — Summary		
Biomarker	Zero-crossing	Sig. CDR-SB
GFAP	2.11	0.5, 1.0
NfL	2.97	None
p-tau181	Not reached	0.5, 1.0, 1.5
p-tau217	2.73	None

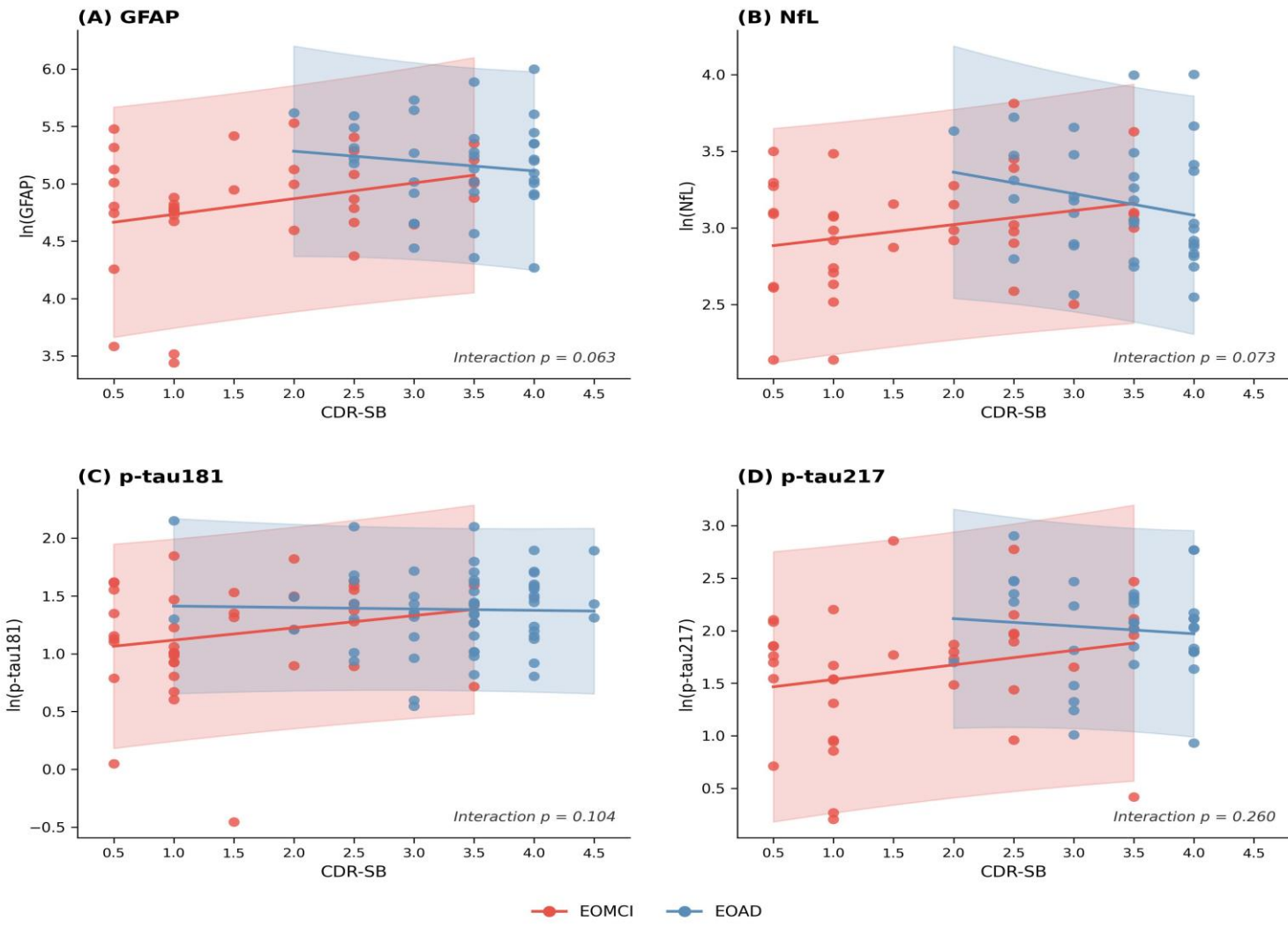
ME = marginal effect of Global CL on log-biomarker; 95% CI from 1,000 bootstrap resamples.

Figure 1. Global Amyloid PET Burden vs. Plasma Biomarkers



Scatter plots of Global Centiloid vs. log-transformed plasma biomarkers by diagnostic stage. Regression lines with 95% CI (adjusted: age, sex, education, APOE ε4). Red ● EOMCI; Blue ● EOAD. Interaction p-values per panel.

Figure 2. Plasma Biomarkers vs. Clinical Severity (CDR-SB)



Scatter plots of log-transformed plasma biomarkers versus CDR-SB. Models were adjusted for age, sex, education, and APOE ε4 status. Positive associations were observed in EOMCI, whereas associations were attenuated or reversed in EOAD-0.5.

METHODS

Participants & Amyloid PET

- LEAF cohort: nationwide, multicenter, Korea (2021–)
- n=104 Aβ(+) at CDR 0.5 (EOMCI 46; EOAD-0.5 58)
- [18F]-FBB or [18F]-FMM; Centiloid quantification (n=86)
- 3-T MRI: T1, FLAIR, SWI; WMH by Fazekas scale

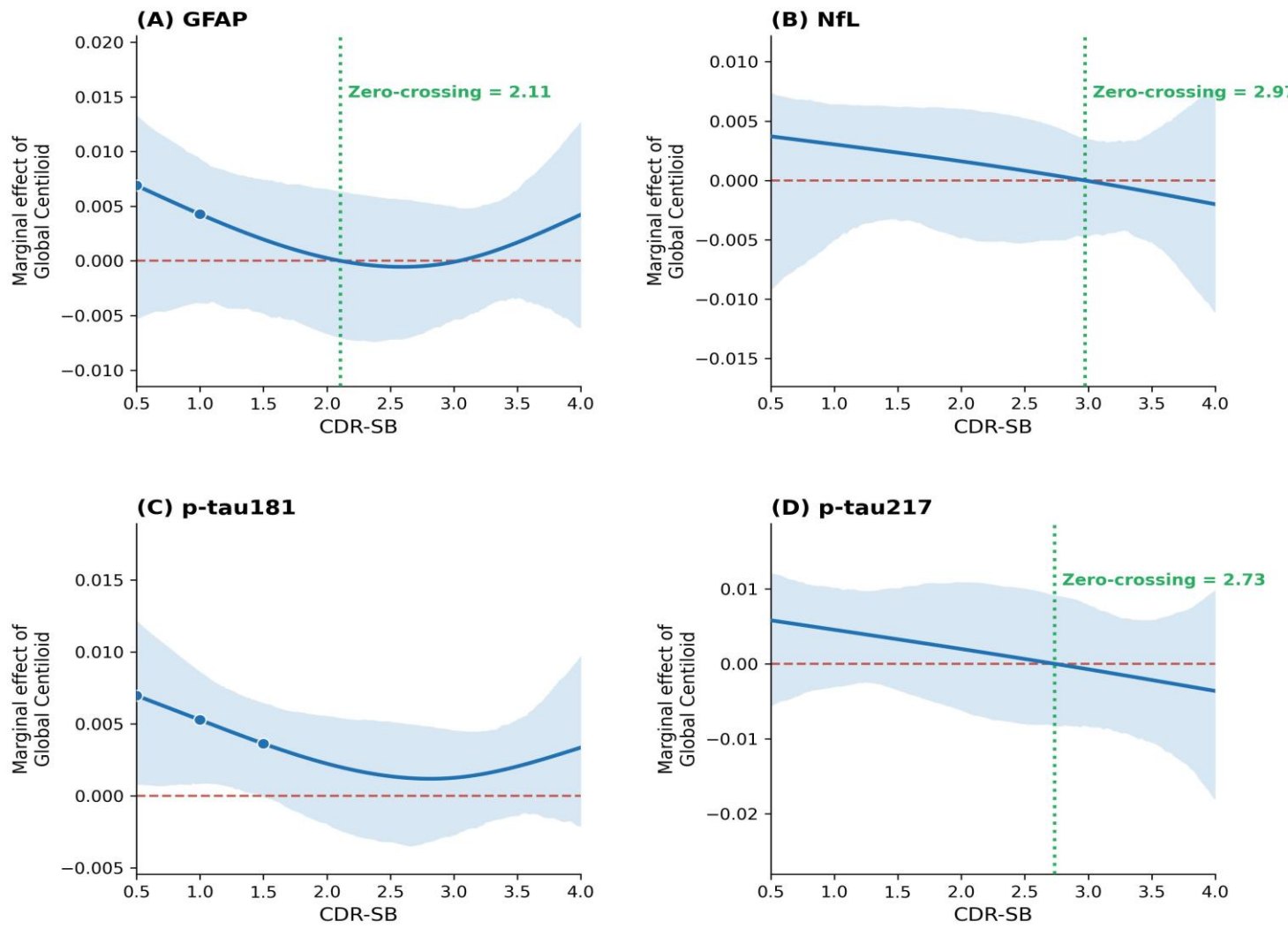
Statistical Analysis (R v4.4.2)

- ① Linear regression: Global CL vs. log-biomarker (by stage)
- ② Linear regression: log-biomarker vs. CDR-SB (by stage)
- ③ RCS models: marginal effects of Global CL across CDR-SB (3 knots; 1,000-bootstrap 95% CI)→ *Covariates: age, sex, education, APOE ε4 (± Global CL)*

Plasma Biomarkers

- NfL, GFAP, p-tau217, Aβ40/42: Simoa 4-Plex E (n=72–73)
- p-tau181: In-house Simoa, Hanyang Univ. (n=103)
- All values natural log-transformed

Figure 3. RCS: Marginal Effects of Global Amyloid PET Burden



Marginal effects of Global CL on log-biomarkers across CDR-SB spectrum (1,000-bootstrap 95% CI). (A) GFAP: zero-crossing CDR-SB 2.11; sig. at 0.5, 1.0. (B) NfL: zero-crossing CDR-SB 2.97; no sig. levels. (C) p-tau181: no zero-crossing; sig. at 0.5, 1.0, 1.5. (D) p-tau217: zero-crossing CDR-SB 2.73; no sig. levels.

► KEY MESSAGE: Amyloid–plasma coupling differs by biomarker even within a uniform CDR 0.5 stage.