



The association between blood-based biomarkers and functional decline varies by baseline cognitive status

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Background

- Blood-based biomarker (BBM) levels vary along the Alzheimer's disease (AD) continuum.
- BBMs correlate with AD pathophysiology and are predictive markers of AD.
- Functional decline is a subjective measure of how cognition impairs daily function and can be a diagnostic marker of AD progression.
- BBMs are associated with functional decline.
- This study aims to characterize the predictive ability of BBMs across varying baseline cognitions to support implementation in clinical practice.

Methods

- Participants:** 334 adults aged ≥ 60 years from the Vanderbilt Memory & Aging Project completed fasting blood draws that quantified plasma phosphorylated-tau231 (p-tau231), Glial Fibrillary Acidic Protein (GFAP), and Neurofilament Light (NfL) using Quanterix Simoa over a mean 7 ± 3 year follow-up period. (See Table 1)
- Assessment:** Self-report, informant-report, and/or clinician judgement. Clinician judgement tests were the Functional Capacities for Activities of Daily Living scale, the Functional Activities Questionnaire, and the Clinical Dementia Rating scale Sum of Boxes.
- Statistical Analysis:** Linear regression models adjusted for age, sex, education, race/ethnicity, APOE $\epsilon 4$ status, modified Framingham Stroke Risk Profile (FRSP), and cognitive copathologies.

Table 1. Participant Characteristics by Baseline Cognition

	Combined (n=334)	Unimpaired (n=175)	Ambiguous at Risk (n=27)	MCI (n=132)	P-value ^a
Age (years)	72.9 $\pm$ 7.3	72.5 $\pm$ 7.2	73.0 $\pm$ 6.3	73.4 $\pm$ 7.6	0.68
Sex (% Male)	59%	59% (104)	74%	56%	0.22
Education (years)	15.9 $\pm$ 2.7	16.4 $\pm$ 2.4	16.3 $\pm$ 2.7	15.1 $\pm$ 2.7	<0.001
Race (% Non-Hispanic White)	87%	87%	85%	86%	0.88
APOE $\epsilon 4$ status (% positive)	34%	29%	22%	44%	0.01
FSRP – age points	6.4 $\pm$ 3.1	6.0 $\pm$ 3.1	7.3 $\pm$ 2.6	6.8 $\pm$ 3.3	0.028
Biomarkers					
Plasma P-tau231 (pg/mL)	6.8 $\pm$ 4.3	6.3 $\pm$ 3.9	6.7 $\pm$ 4.1	7.6 $\pm$ 4.8	0.046
Plasma GFAP (pg/mL)	183 $\pm$ 99	159 $\pm$ 87	183 $\pm$ 79	216 $\pm$ 109	<0.001
Plasma NfL (pg/mL)	30 $\pm$ 21	25 $\pm$ 13	26 $\pm$ 12	38 $\pm$ 28	<0.001
Functional Tests					
FC-ADL	59.6 $\pm$ 11.6	54.9 $\pm$ 6.1	62.9 $\pm$ 12.4	65.3 $\pm$ 14.0	<0.001
FAQ	1.31 $\pm$ 2.24	0.097 $\pm$ 0.316	1.56 $\pm$ 1.50	2.87 $\pm$ 2.77	<0.001
CDR Sum of Boxes	0.491 $\pm$ 0.772	0.006 $\pm$ 0.053	0.833 $\pm$ 0.519	1.06 $\pm$ 0.888	<0.001

Note. FSRP= Framingham Stroke Risk Profile. GFAP=Glial Fibrillary Acidic Protein. NfL=Neurofilament Light Chain. FC-ADL=Functional Capacities for Activities of Daily Living scale. FAQ=Functional Activities Questionnaire. CDR=Clinical Dementia Rating. Values are the mean $\pm$ standard deviations. An asterisk denotes results derived from Wilcoxon tests for continuous variables or chi-squared tests for categorical variables. P-values <0.05 were considered significant.

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Results

- All three BBMs were associated with longitudinal trajectories of each of the three functional outcomes. (p-values<0.0003) (See Table 1)
- Higher baseline BBM levels associated with faster functional decline.
- P-tau231 and NfL correlations did **not** differ significantly across baseline cognitive status groups. (p-values>0.06)
- GFAP interacted more closely with MCI participants than cognitively unimpaired participants. (p-values $\leq$ 0.004) (See Figure 1)

Figure 1. Baseline cognition affecting the correlation of GFAP with annual functional decline

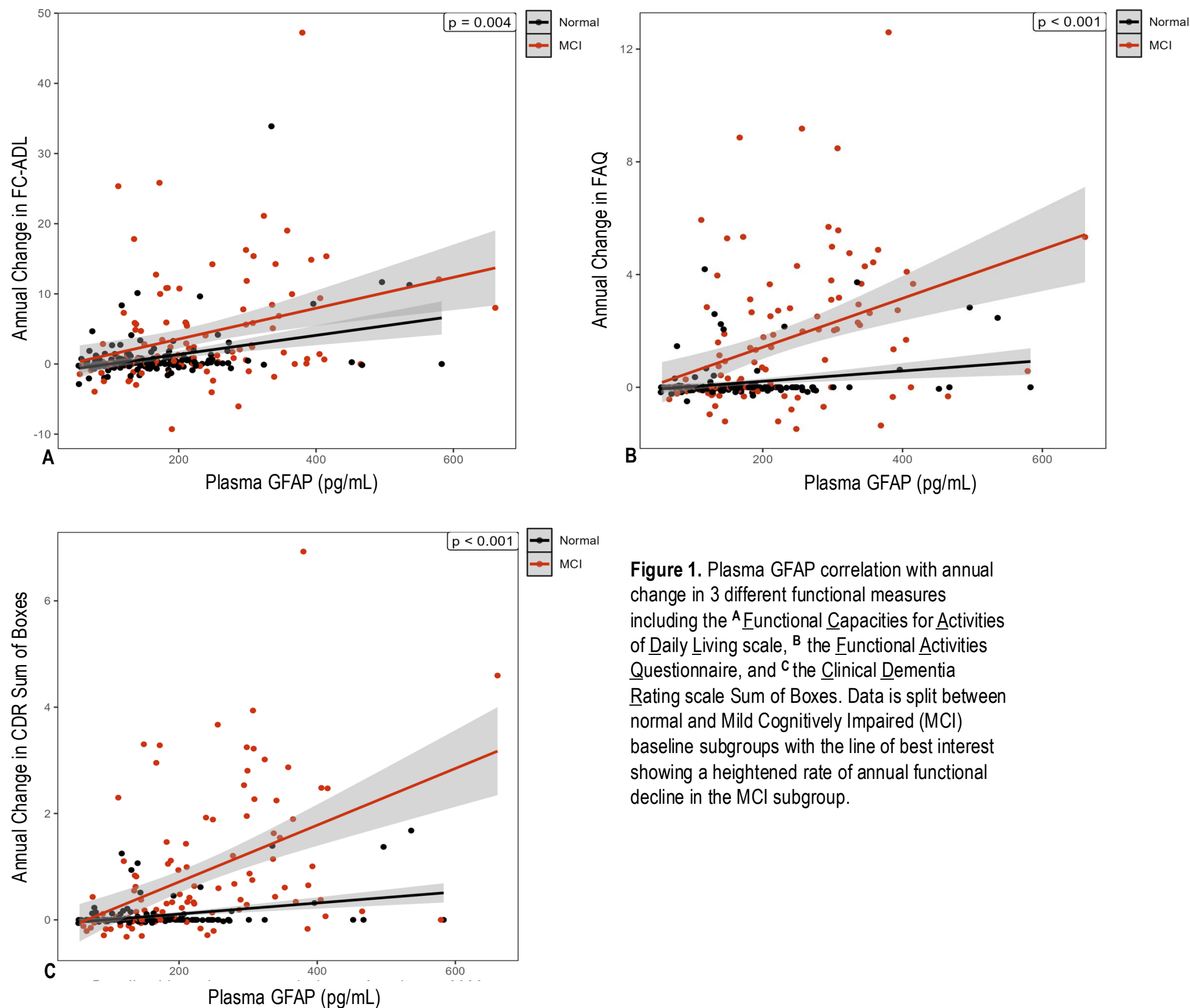


Figure 1. Plasma GFAP correlation with annual change in 3 different functional measures including the ^AFunctional Capacities for Activities of Daily Living scale, ^B the Functional Activities Questionnaire, and ^C the Clinical Dementia Rating scale Sum of Boxes. Data is split between normal and Mild Cognitively Impaired (MCI) baseline subgroups with the line of best interest showing a heightened rate of annual functional decline in the MCI subgroup.

Conclusions

- All three BBMs were predictive markers for functional decline.
- Plasma p-tau231 and NfL assessed functional decline similarly in the cognitively impaired and cognitively unimpaired subgroups.
- Plasma GFAP assessed functional decline more strongly in cognitively impaired (MCI) participants versus cognitively unimpaired participants.
- Current functional status should be considered when assessing plasma GFAP relevance.
- Understanding BBM association with cognitive diagnosis is relevant for incorporating BBMs in clinical diagnoses.