

BACKGROUND

- In frontotemporal lobar degeneration (FTLD) due to Tau (FTLD-Tau) and TDP-43 (FTLD-TDP) pathologies, multiple studies have demonstrated the prognostic utility of plasma neurofilament light (NfL),¹⁻³ an axonal biomarker that can predict faster cognitive decline.
- Findings on the utility of plasma glial fibrillary acidic protein (GFAP), a measure of reactive astrocytes, in FTLD are mixed.
- Study designs have focused primarily on participants with FTLD-associated genetic variants,⁴ and there is limited study of plasma GFAP in symptomatic sporadic FTLD, where autopsy is needed to confirm diagnosis.
- Indeed, postmortem histopathology data implicates neuroinflammation a key contributor to cognitive impairment in FTLD.
- We sought to test whether plasma GFAP has added utility when tracking disease progression in symptomatic FTLD when accounting for plasma NfL.

METHODS

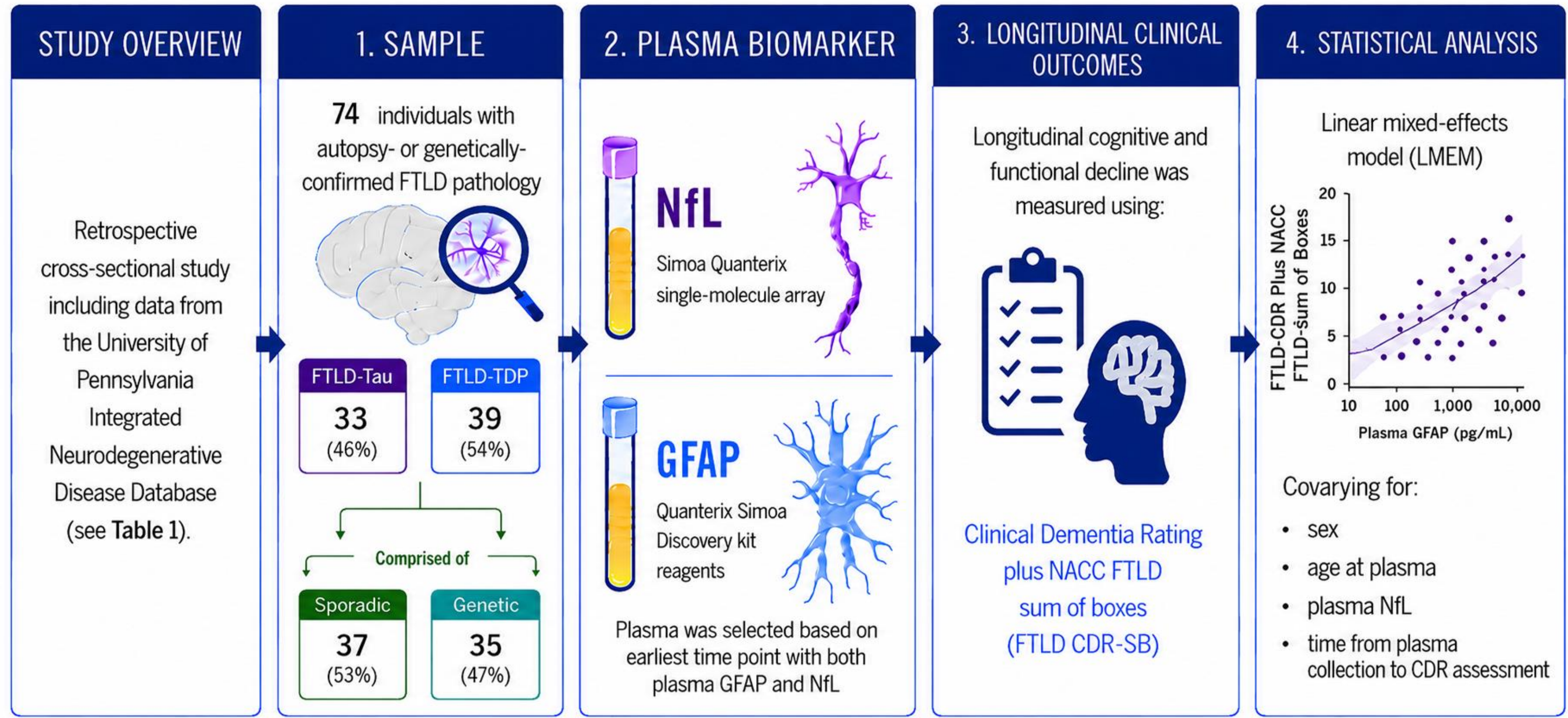
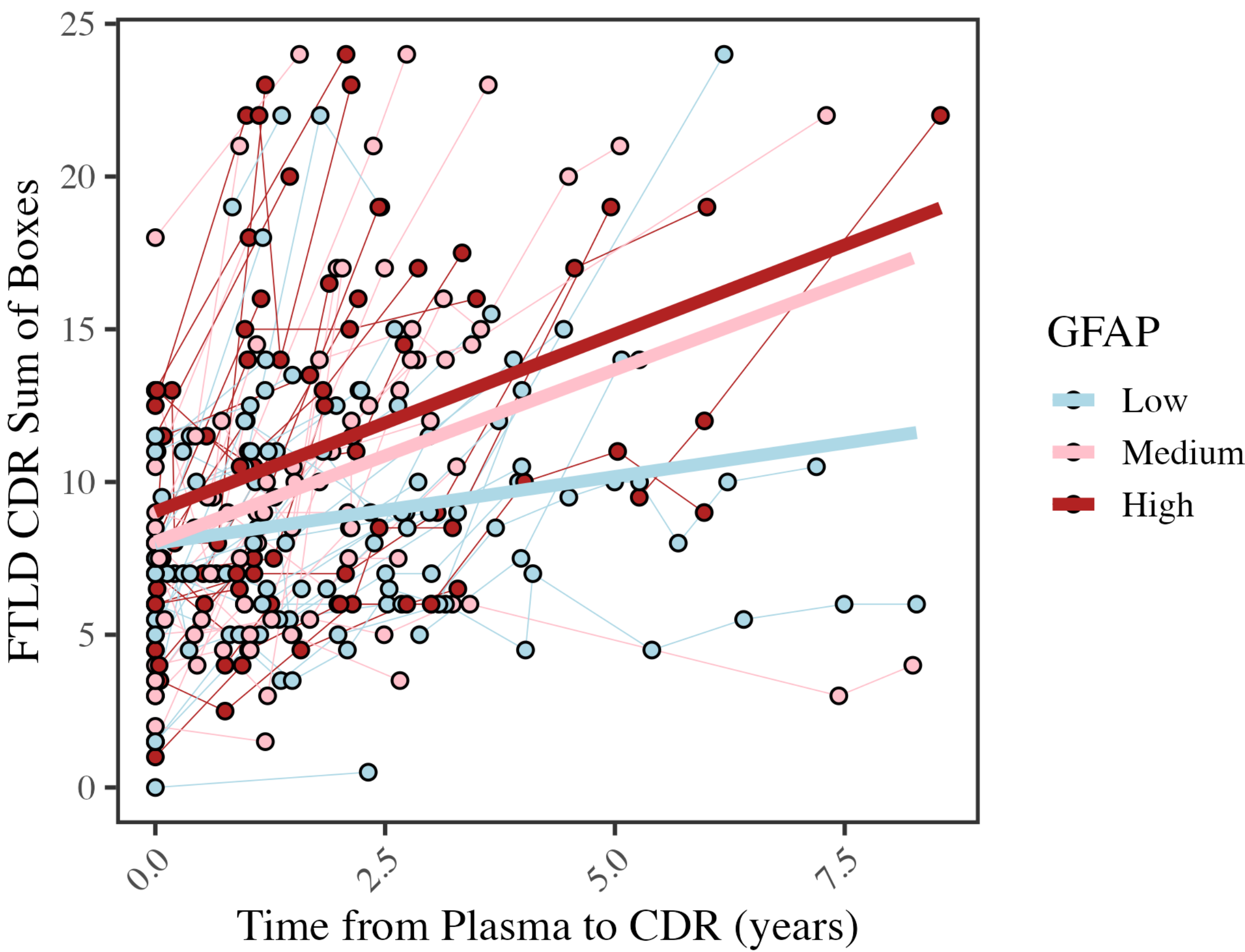


Figure 1. Plasma GFAP was split into tertiles for visualization; two cases with intermediate ADNC were excluded. All time variables are measured in years.

RESULTS

	FTLD-Tau	FTLD-TDP	p-value	Missing
N	33	39		
Plasma GFAP (pg/mL)	121.8 [86.9, 165.5]	105.4 [61.8, 149.6]	0.150	--
Plasma NfL (pg/mL)	34.5 [26.2, 46.0]	33.8 [20.4, 59.7]	0.777	2
Age at Plasma (Years)	67.0 [58.0, 72.0]	63.0 [55.5, 66.5]	0.101	--
Sex = Male (%)	21 (63.6%)	27 (69.2%)	0.802	--
Plasma to FTLD-CDR (Years)	0.0 [0.0, 0.6]	0.0 [0.0, 0.1]	0.259	--
First FTLD-CDR Score	7.5 [5.0, 11.0]	7.0 [5.2, 10.2]	0.537	--
Disease Duration (Years)	9.0 [6.8, 11.0]	7.0 [5.0, 11.0]	0.334	11
Genetic Status (%)	9 (27.3%)	26 (66.7%)	0.002	--
ADNC = Low (%)	13 (52.0%)	7 (38.9%)	0.589	29
Phenotype (%)			0.028	--
ALS/MND	0 (0.0%)	6 (15.4%)		
Amnesic	1 (3.0%)	1 (2.6%)		
Behavioral variant FTD	14 (42.4%)	23 (59.0%)		
Unspecified FTD	3 (9.1%)	1 (2.6%)		
Corticobasal syndrome	5 (15.2%)	1 (2.6%)		
Progressive supranuclear palsy	2 (6.1%)	0 (0.0%)		
Lewy Body Spectrum Disorder	1 (3.0%)	0 (0.0%)		
Logopenic PPA	1 (3.0%)	0 (0.0%)		
Non-fluent PPA	5 (15.2%)	2 (5.1%)		
Semantic variant PPA				
PPA NOS	0 (0.0%)	3 (7.7%)		

Table 1. ALS/MND = Amyotrophic Lateral Sclerosis/ Motor Neuron Disease; NOS = not otherwise specified; PPA = Primary Progressive Aphasia; Genetic status, FTLD-TDP: C9orf72 = 17, GRN = 6, TARDBP = 2, TBK1 = 1; FTLD-Tau: MAPT = 8, VCP =1.



Longitudinal CDR – All FTLD	β	95%CI	p-value
Log (Plasma GFAP)	-1.522	-4.139 – 1.095	0.2580
Time from Plasma to CDR (Years)	-3.521	-5.765 – -1.276	0.0023
Log (Plasma NfL)	2.881	1.003 – 4.758	0.0038
Pathology = FTLD-TDP	-2.160	-4.116 – -0.204	0.0344
Sex = Male	-0.812	-3.183 – 1.558	0.5043
Age at Plasma (Years)	-0.065	-0.186 – 0.055	0.2920
log(Plasma GFAP)*Time from Plasma to CDR	1.109	0.619 – 1.599	<0.0001

Longitudinal CDR – FTLD Tau	β	95%CI	p-value
Log (Plasma GFAP)	3.310	-2.195 – 8.815	0.2473
Time from Plasma to CDR (Years)	-0.558	-7.103 – 5.988	0.8678
Log (Plasma NfL)	-2.129	-7.098 – 2.839	0.4086
Sex = Male	-0.901	-4.487 – 2.686	0.6267
Age at Plasma (Years)	-0.285	-0.483 – -0.087	0.0088
log(Plasma GFAP)*Time from Plasma to CDR	0.653	-0.747 – 2.052	0.3631

Longitudinal CDR – FTLD TDP	β	95%CI	p-value
Log (Plasma GFAP)	-2.141	-4.976 – 0.694	0.1465
Time from Plasma to CDR (Years)	-2.917	-5.232 – -0.603	0.0146
Log (Plasma NfL)	3.484	1.729 – 5.24	0.0005
Sex = Male	-2.283	-5.347 – 0.781	0.1533
Age at Plasma (Years)	0.077	-0.072 – 0.225	0.3208
log(Plasma GFAP)*Time from Plasma to CDR	0.911	0.403 – 1.42	0.0006

CONCLUSION

High levels of plasma GFAP are associated with worse performance over time on FTLD-CDR Sum of Boxes, even when accounting for plasma NfL, a biomarker known to have utility in predicting cognitive and functional outcomes in FTLD. When stratified by FTLD-subtypes, these results remained statistically significant in FTLD-TDP.

1. Plasma GFAP may be a useful prognostic biomarker of faster clinical decline in FTLD.
2. Neuroinflammation likely has an independent contribution to clinical symptoms, and may be an avenue for treatment, especially in FTLD-TDP.
3. Future work will: A) confirm findings in domain-specific neuropsychological testing data, and B) separately interrogate sporadic and genetic groups, as well as C) clinical pathological subgroups (e.g., behavioral variant FTD, 3R Tau vs 4R Tau etc.).

REFERENCES

1. Giannini, Lucia AA, et al. "Clinical value of longitudinal serum neurofilament light chain in prodromal genetic frontotemporal dementia." *Neurology* 101.10 (2023): e1069-e1082.
2. Cousins, Katheryn AQ, et al. "Distinguishing frontotemporal lobar degeneration tau from TDP-43 using plasma biomarkers." *JAMA neurology* 79.11 (2022): 1155-1164.
3. Gendron, Tania F et al. "Comprehensive cross-sectional and longitudinal analyses of plasma neurofilament light across FTD spectrum disorders." *Cell reports. Medicine* vol. 3,4 100607. 19 Apr. 2022, doi:10.1016/j.xcrm.2022.100607
4. Sheth, Udit et al. "Comprehensive cross-sectional and longitudinal comparisons of plasma glial fibrillary acidic protein and neurofilament light across FTD spectrum disorders." *Molecular neurodegeneration* vol. 20,1 30. 12 Mar. 2025, doi:10.1186/s13024-025-00821-4

ACKNOWLEDGMENTS

This study was funded by P01-AG066597, R01-AG087258, University of Pennsylvania Alzheimer's Disease Research Center, and the Penn Institute on Aging. We would like to thank participants and their families for their research participation.

Contact Information: Sheina.Emrani@pennmedicine.upenn.edu
Katheryn Cousins: Katheryn.Cousins@pennmedicine.upenn.edu