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Background

- Alzheimer's disease (AD) is characterized by amyloid- β plaques, tau neurofibrillary tangles, and neurodegeneration.
- Despite advances in amyloid and tau biomarkers, reliable biofluid markers of neurodegeneration remain limited.
- Neurofilament light chain (NfL), the most widely used marker, lacks AD specificity, reflects general axonal injury, and is influenced by both central and peripheral sources.

Objective

- To identify plasma biomarkers that more specifically reflect neurodegeneration by associations with structural brain changes in AD and progression to clinical decline.

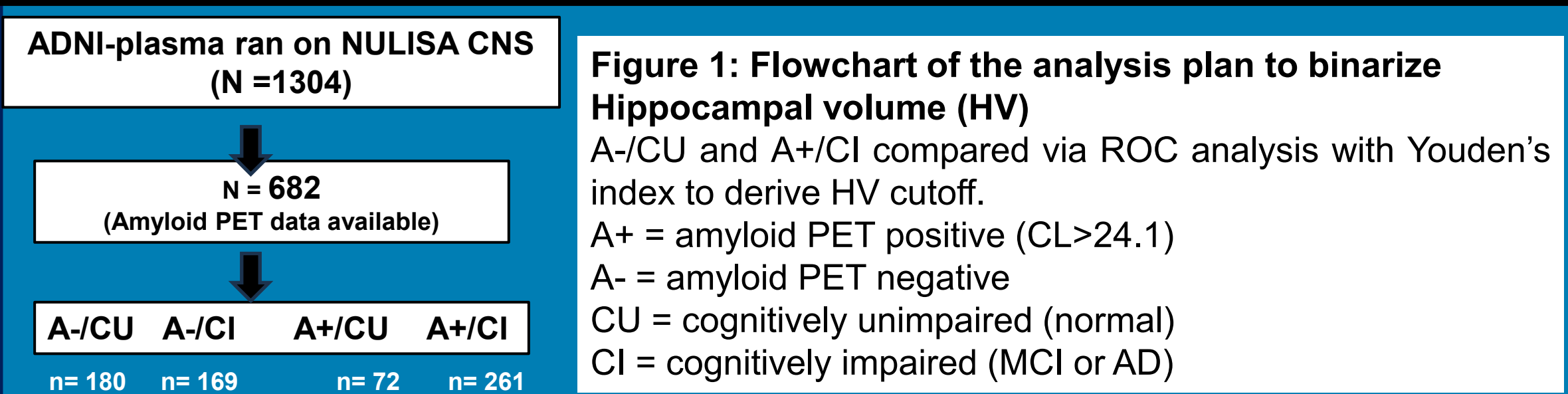
Methods

- We employed Nucleic Acid-Linked Immuno-Sandwich Assay (NULISA™) CNS panel to measure 1,304 plasma samples from participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Table 1).
- The study included 1,304 participants with baseline plasma and baseline/longitudinal MRI data.
- Linear regression and linear mixed-effects models examined cross-sectional and longitudinal associations between baseline plasma biomarkers and hippocampal volume, while adjusting for age, sex, education, APOE ϵ 4 status, and intracranial volume.
- Binarized hippocampal volume (Figure 1) were analyzed via Cox regression to identify baseline plasma biomarkers associated with neurodegeneration.

Characteristic	Control N = 487 ¹	MCI N = 614 ¹	AD N = 203 ¹
Age	72.79 (6.31)	72.32 (7.61)	74.53 (7.96)
Gender			
Male	197 (40%)	359 (58%)	121 (60%)
Female	290 (60%)	255 (42%)	82 (40%)
Education	16.65 (2.52)	16.14 (2.72)	15.54 (2.92)
APOE_score			
carrier	152 (31%)	294 (48%)	144 (71%)
non carrier	335 (69%)	320 (52%)	59 (29%)
MMSCORE	29.11 (1.12)	27.73 (1.87)	23.15 (2.17)

¹Mean (SD); n (%)

Table 1: Demographics of the ADNI plasma samples.



Results

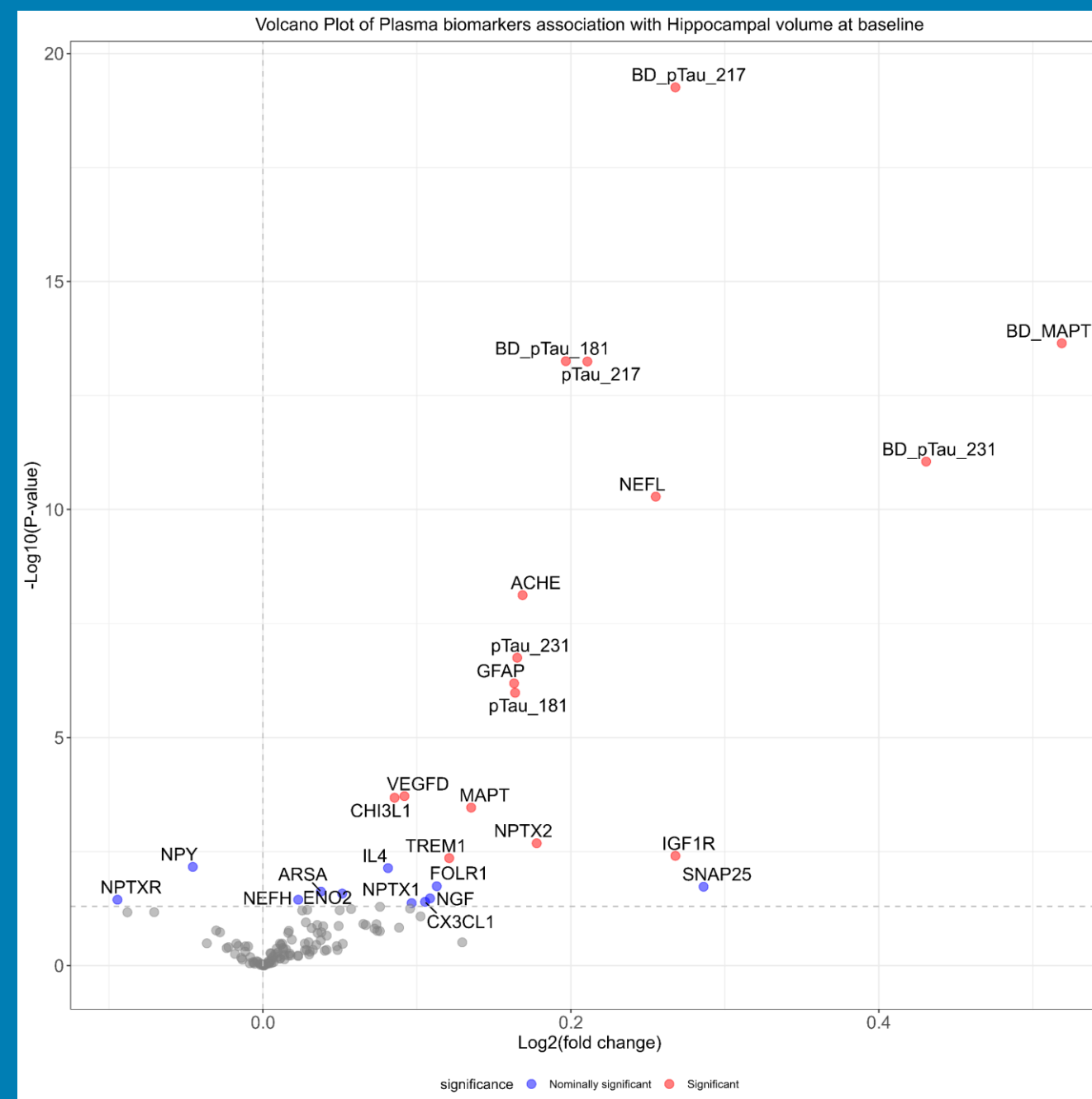


Figure 2: Baseline plasma biomarker associations with hippocampal volume. Volcano plots showing differences in protein alterations in cerebrospinal fluid (CSF) showing associations with hippocampal volume in the ADNI cohort at baseline. Blue dots indicate proteins nominally significant ($p < 0.05$ but $p_{adj} > 0.05$) while red dots are significant after multiple-testing correction ($p_{adj} < 0.05$). The horizontal dashed line indicates the unadjusted p-value threshold of 0.05.

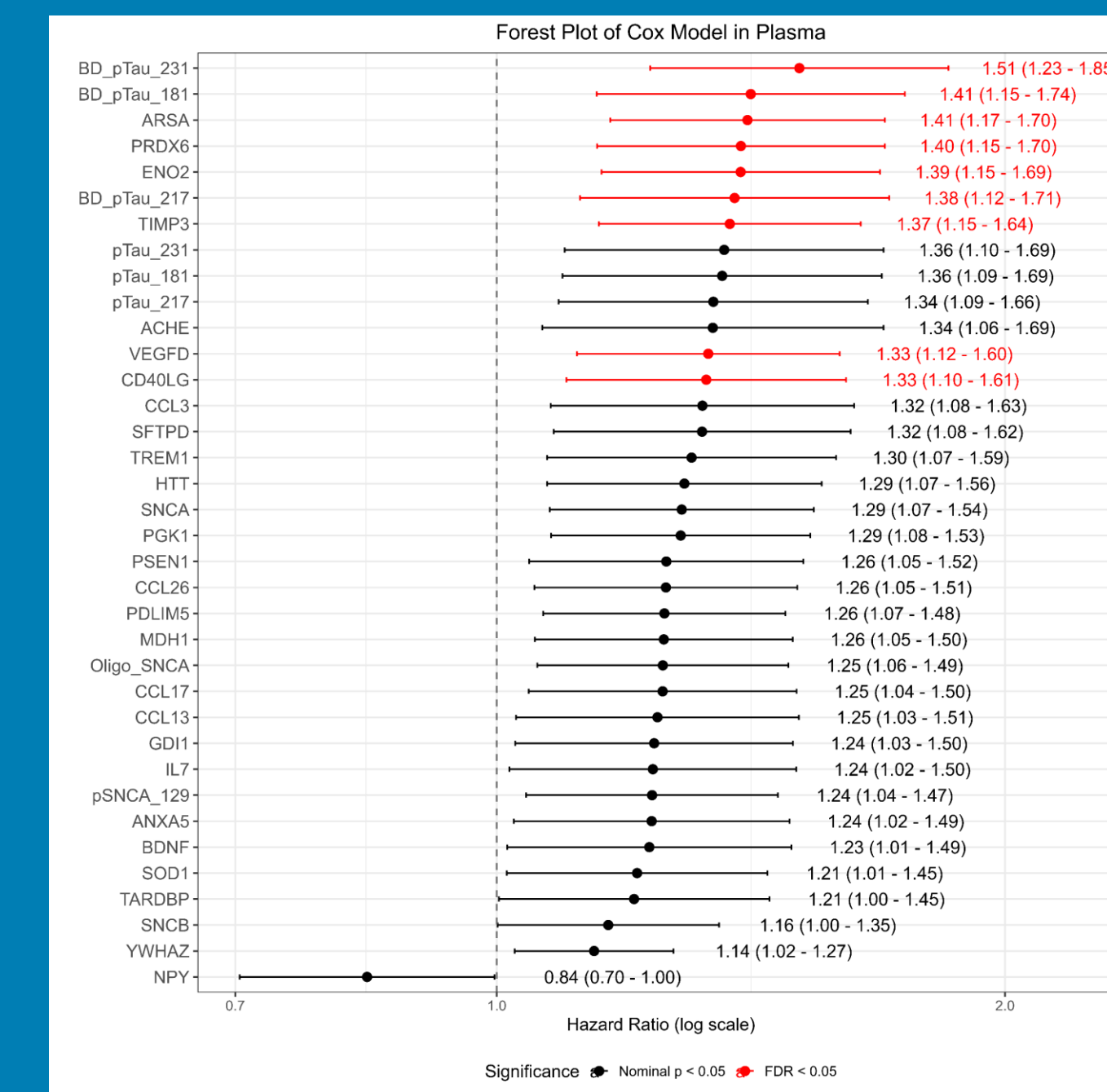


Figure 5: Associations of significant plasma biomarkers with binarized hippocampal volume in Cox regression models. Forest plot of significant CSF biomarkers identified from the cox regression model following hippocampal volume binarization. The hazard ratios (log scale) and the 95% CI are shown on the x-axis while the significant biomarkers are listed on the y-axis.



Figure 3: Baseline biomarker associations with longitudinal change in hippocampal volume. Volcano plots illustrating associations between baseline plasma protein levels and longitudinal hippocampal volume loss in the ADNI cohort. The x-axis denotes effect sizes corresponding to time $\times$ protein interaction terms derived from linear mixed-effects models.

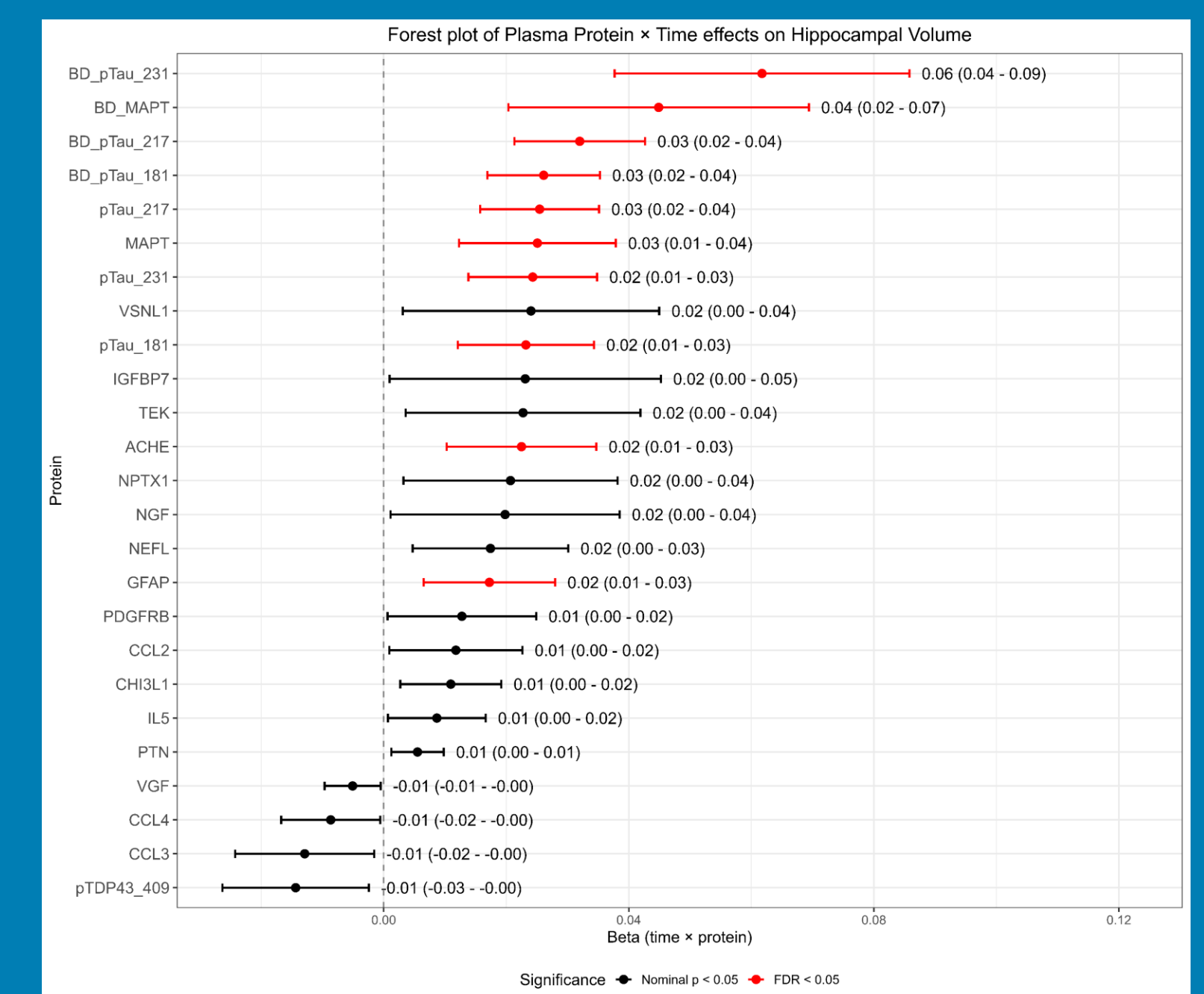


Figure 4: Longitudinal associations between significant plasma biomarkers and hippocampal volume loss.

Forest plot of significant CSF biomarkers associated with longitudinal hippocampal volume loss. Beta coefficients for the time $\times$ protein interaction terms from linear mixed-effects models, along with 95% confidence intervals, are displayed on the x-axis, and significant biomarkers are listed on the y-axis.

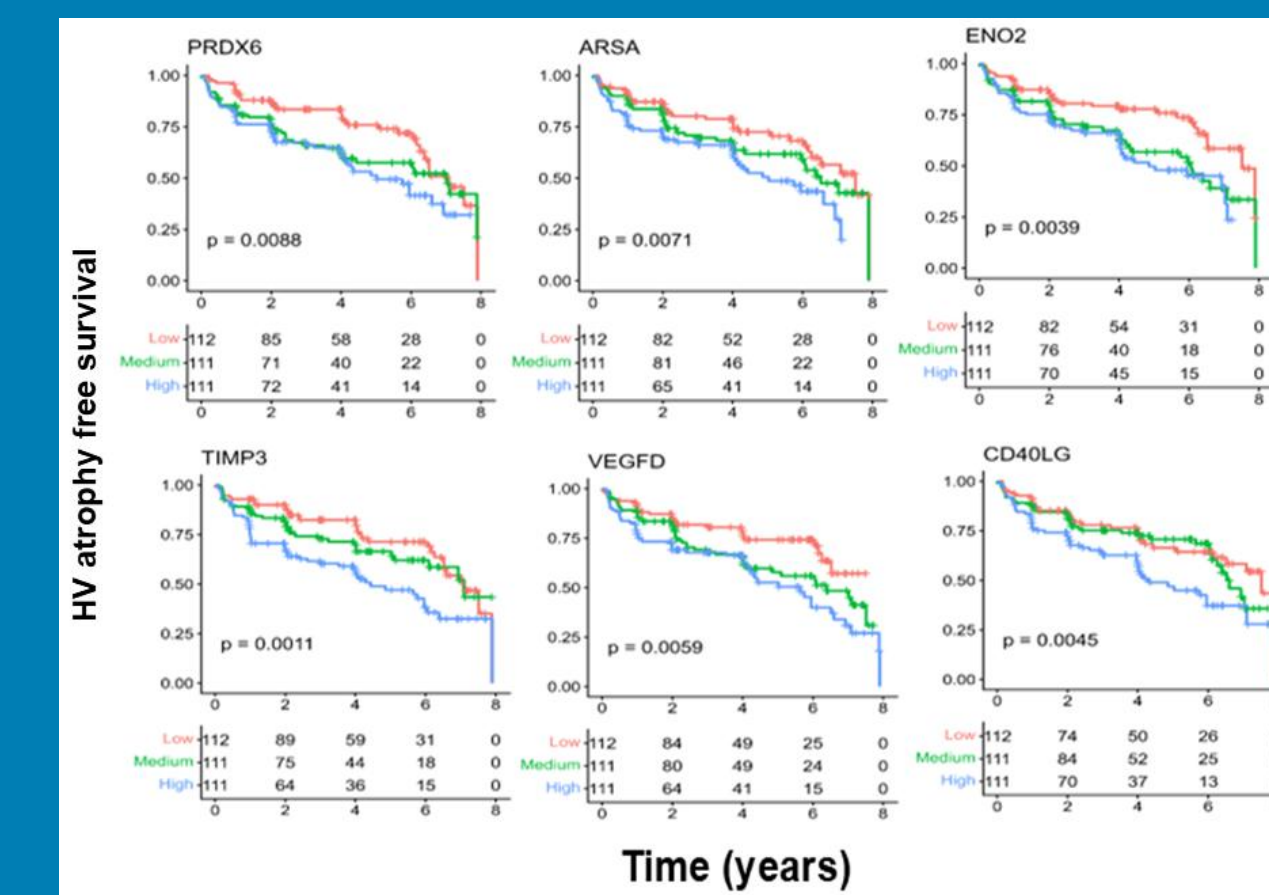


Figure 6: Kaplan-Meier analyses of significant plasma biomarkers associated with hippocampal volume atrophy.

Kaplan-Meier plots of the significant plasma biomarkers from the cox-proportional hazard model are plotted. The follow-up time in years from baseline is plotted on the x-axis, while the probability of the HV atrophy free survival is plotted on the y-axis. The biomarkers are stratified into tertiles (low, medium, high) with corresponding risk tables displayed below each plot.

✓ We observed that brain-derived versions of phospho-tau (BD-pTau217, BD-pTau231, BD-pTau181), NEFL, GFAP, AChE, VEGFD, BD-MAPT, CH3L1, IGF1R, TREM1, NPTX2 were positively associated with hippocampal volume cross-sectionally.

✓ Similar profile (BD-pTau217, BD-pTau231, BD-pTau181, BD-MAPT, AChE, GFAP) were observed for longitudinal associations between plasma biomarkers and hippocampal volume loss. NFL lost significance as a prognostic marker though.

✓ We binarized the hippocampal volume following our approach as in Figure 1, performed cox proportional hazard regression modeling and observed that only brain-derived versions of phospho-tau along with ARSA, PRDX6, ENO2, VEGFD, CD40LG, TIMP3 had significantly higher hazard ratio for hippocampal atrophy.

Conclusion

- Brain-derived versions of phospho-tau show strong and consistent association with hippocampal atrophy cross-sectionally and longitudinally.
- We found that increased levels of plasma proteins related to inflammation (CD40LG), blood brain barrier dysfunction (VEGFD), redox balance (PRDX6), neuronal metabolism (ENO2), lipid homeostasis (ARSA) and cytoskeletal stability (TIMP3) were at a higher risk for hippocampal atrophy or neurodegeneration.
- Further work will be required to replicate these findings in an independent dataset.