

High Sensitivity CNS and Inflammation Proteomics for Predicting Dementia in Older Adults with Diabetes: ARIC Cohort



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BACKGROUND

- Proteomics can provide insight into mechanisms linking diabetes to dementia risk
- Brain derived forms of p-tau are emerging as stronger cross-sectional discriminators of dementia and brain amyloid but prospective data are limited
- Highly sensitive and specific proteomic panels provide a growing coverage of candidate proteins.

GOALS

- To describe blood biomarkers of dementia incidence in diabetes
- To compare different AD biomarkers, particularly brain derived (BD) vs. total p-tau isoforms
- To explore the added value of inflammatory biomarkers to CNS & AD biomarkers

METHOD

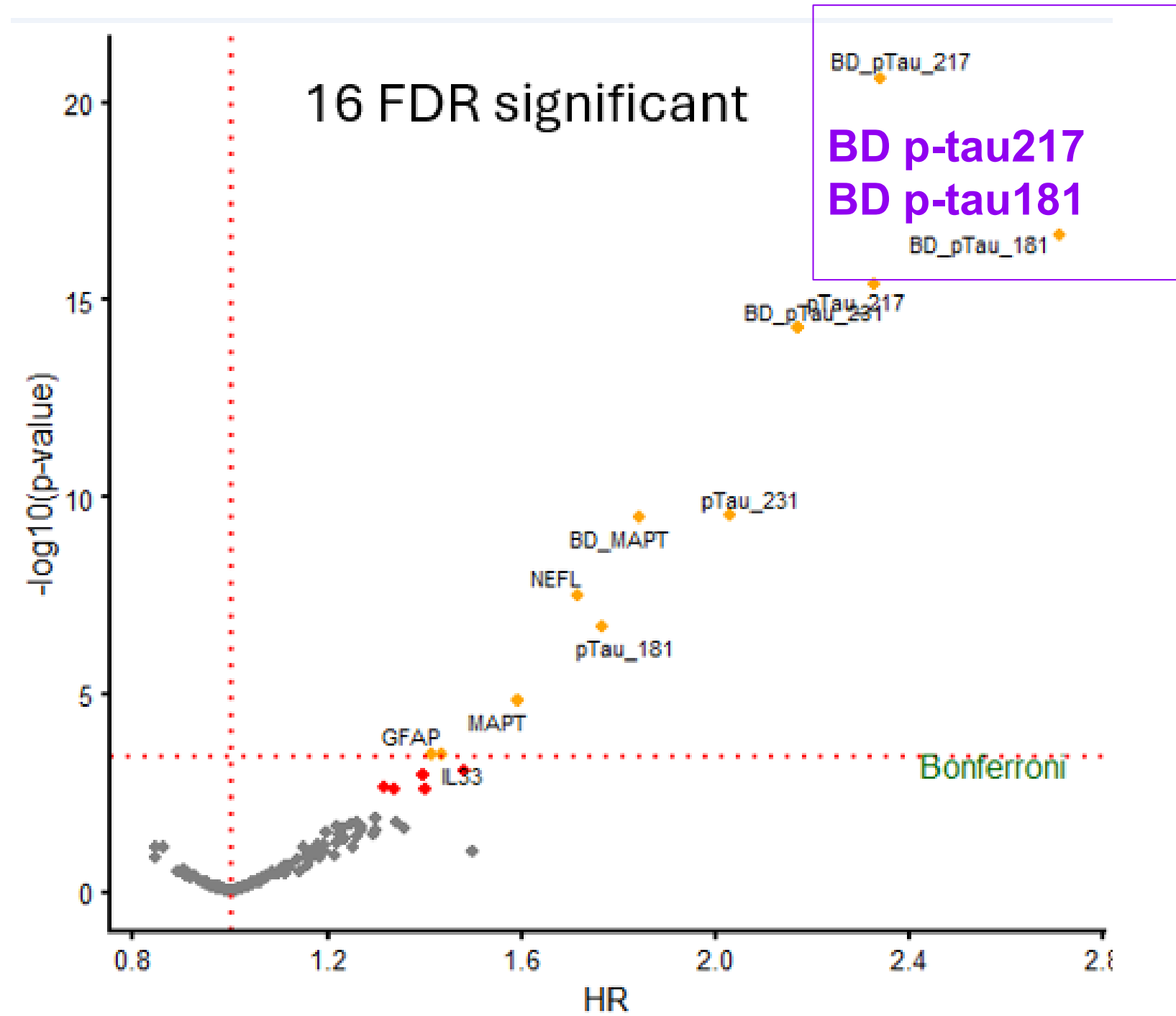
- Prospective cohort study of 485 ARIC Study participants with diabetes (age 58-84y, 47% women, 34% Black) in 2005-06.
- ~15 years of follow-up
- 135 new dementia cases
- Biomarkers measured on frozen specimen using the Alamar NULISA assay at UMN ARDL lab
 - CNS panel – 131 proteins
 - Inflammation panel – 249 proteins
- Cox proportional hazards model for dementia incidence

Baseline Characteristics

Characteristic	Overall (N=485)
Age, years	71 (6)
Women	47%
Black race	34%
eGFR, mL/min/1.73m ²	74 (20)
≥1 APOE ε4 allele	32%
HbA1c ≥7%	26%
Diabetes duration ≥10 years	46%
Diabetes medication use	66%
Insulin	18%
Sulfonylurea	26%
Metformin	28%

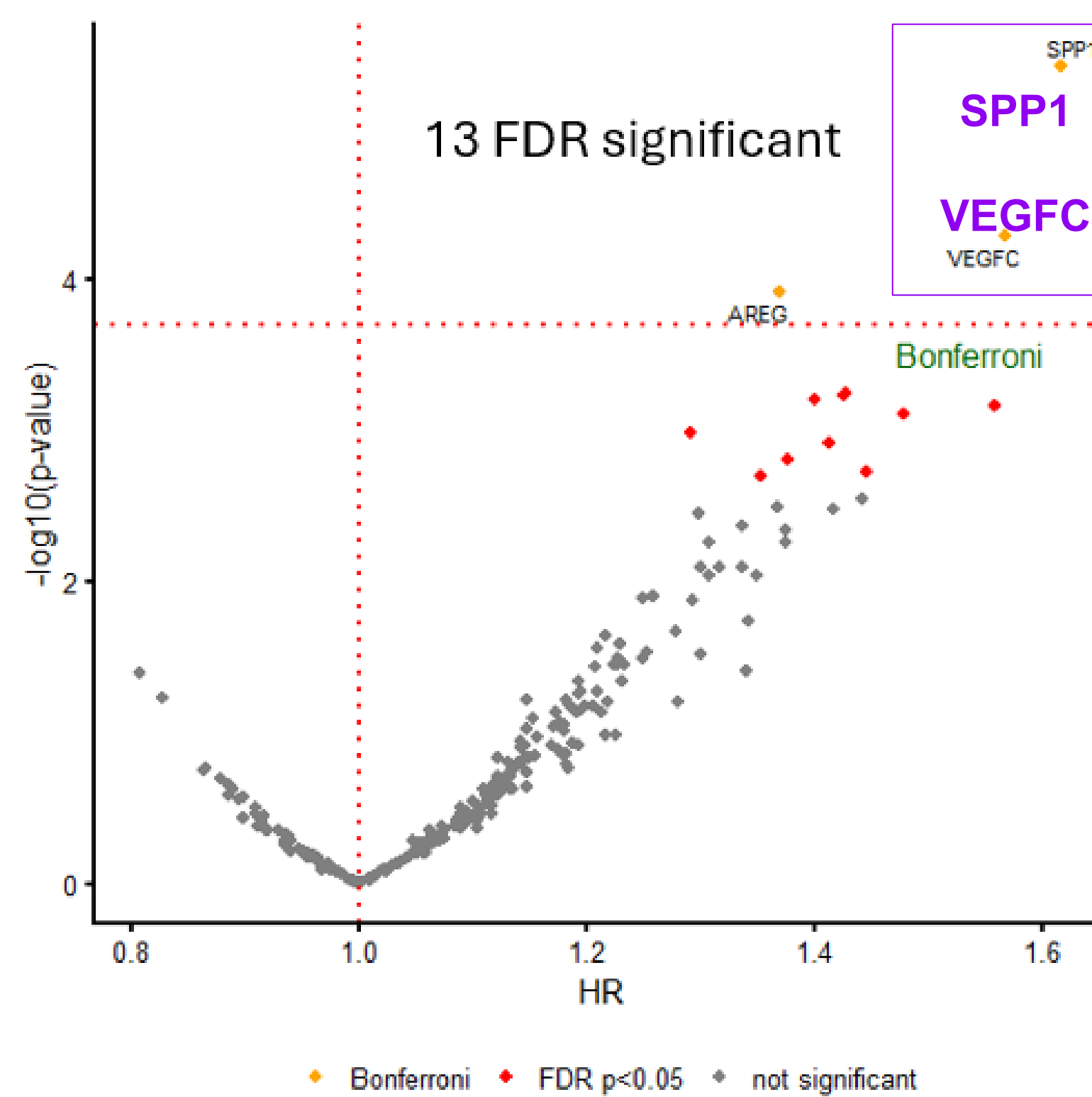
Plasma protein associations with incident dementia after multivariable adjustment*: Volcano plots and table with effect estimates for top proteins

A. CNS Panel



Protein	HR (95% CI)	P-value	FDR	Function/Classification
BD_pTau_217	2.34 (1.96, 2.79)	2E-21	3E-19	Amyloid & Tau Pathology
BD_pTau_181	2.71 (2.15, 3.41)	2E-17	2E-15	Amyloid & Tau Pathology
pTau_217	2.33 (1.90, 2.85)	4E-16	2E-14	Amyloid & Tau Pathology
BD_pTau_231	2.17 (1.79, 2.63)	5E-15	2E-13	Amyloid & Tau Pathology
pTau_231	2.03 (1.63, 2.53)	3E-10	7E-09	Amyloid & Tau Pathology
BD_MAPT	1.84 (1.52, 2.23)	3E-10	7E-09	Amyloid & Tau Pathology
NEFL	1.72 (1.42, 2.08)	3E-08	6E-07	Neurodegeneration
pTau_181	1.77 (1.43, 2.19)	2E-07	3E-06	Amyloid & Tau Pathology
MAPT	1.59 (1.29, 1.97)	2E-05	2E-04	Amyloid & Tau Pathology
GFAP	1.41 (1.17, 1.71)	3E-04	4E-03	Inflammation
IL33	1.44 (1.18, 1.75)	3E-04	4E-03	Inflammation
CALB2	1.48 (1.18, 1.87)	9E-04	1E-02	Neurodegeneration
IGF1R	1.40 (1.14, 1.70)	1E-03	1E-02	Inflammation
CXCL10	1.32 (1.10, 1.58)	2E-03	2E-02	Inflammation
IGFBP7	1.34 (1.11, 1.62)	3E-03	2E-02	Amyloid & Tau Pathology
IL16	1.40 (1.13, 1.75)	3E-03	2E-02	Inflammation

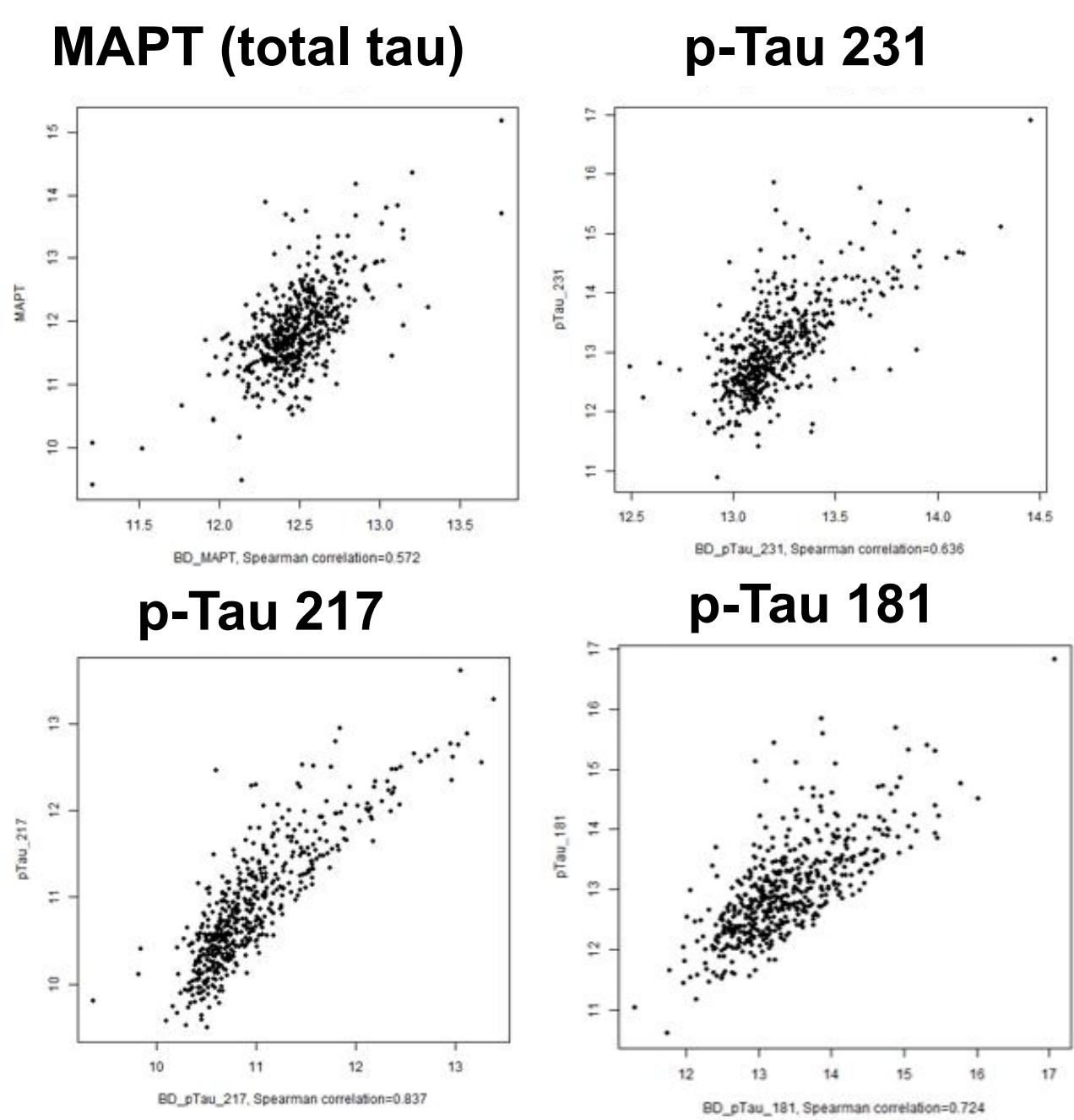
B. Inflammation Panel



Protein	HR (95% CI)	P-value	FDR	Function/Classification
SPP1	1.62 (1.32, 1.98)	4E-06	1E-03	Cytokines
VEGFC	1.57 (1.26, 1.95)	5E-05	6E-03	Growth Factor
AREG	1.37 (1.17, 1.61)	1E-04	1E-02	Growth Factor
CXCL9	1.43 (1.17, 1.75)	6E-04	2E-02	Chemokines
KITLG	1.42 (1.16, 1.74)	6E-04	2E-02	Other
IL33	1.40 (1.15, 1.70)	6E-04	2E-02	Cytokines
CD40	1.56 (1.21, 2.01)	7E-04	2E-02	Receptor
CD4	1.48 (1.18, 1.86)	8E-04	2E-02	Receptor
MMP8	1.29 (1.11, 1.50)	1E-03	3E-02	Other
CD83	1.41 (1.15, 1.74)	1E-03	3E-02	Regulation
MMP1	1.38 (1.13, 1.68)	2E-03	4E-02	Other
CD46	1.44 (1.15, 1.82)	2E-03	4E-02	Regulation
IL17A_IL17F	1.35 (1.12, 1.64)	2E-03	4E-02	Cytokines

Figure 1 abbreviations: FDR, false discovery rate; CNS, central nervous system; BD, brain-derived; ARIC, Atherosclerosis Risk in Communities. Proteins are rank-based inverse normal transformed (interpreted per 1 SD). *Adjusted for age, sex, eGFRcr, race-center, education, APOE4 allele status, body mass index, physical activity, smoking status, hypertension, prevalent stroke, and prevalent coronary heart disease. Orange dots refer to proteins meeting statistical significance based on FDR q<0.05 and Bonferroni-corrected p-value <0.05/(131 or 249); red dots refer to proteins meeting statistical significance based only on FDR q<0.05.

Scatter plots of total vs. brain derived (BD) tau in plasma



- Moderate correlations for the brain-derived vs. non brain-derived plasma tau

RESULTS

- Brain-derived pTau217 and pTau181 associated with highest dementia risk per 1 SD.
- **Dementia incidence discrimination improvement** in diabetes (should be replicated):
 - C statistic of 0.86 [Δ C 0.12, p=3e-9]** for 37 CNS & Inflammation FDR significant proteins clinical covariates alone (C statistic 0.75)
 - 0.83 adding CNS only
 - 0.79 adding inflammation only

CONCLUSIONS

- We identified blood protein measures on the NULISA platform which improved discrimination prediction of incident dementia in persons with diabetes and provide mechanistic insight spanning AD and inflammation markers.
- Brain derived p-tau isoforms were more strongly associated with dementia incidence than total levels of the same isoforms; BD p-tau 217 and 181 were the strongest risk factors.

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