Plasma Phosphorylated Tau 217 in Sporadic Early-Onset Alzheimer's Disease:
Associations with Tau PET, Amyloid PET, and Clinical Progression

Renaud La Joie, **Marlene Lin**, Ganna Blazhenets, Ani Eloyan, Piyush Maiti, Zoe Lin, Dustin Hammers, Robert Koeppe, Maria Carrillo, Bradford Dickerson, Liana Apostolova, Gil Rabinovici, Jeffrey Dage, for the LEADS consortium

AIMS

1. **Assess diagnostic performance** of baseline plasma phosphorylated-tau217 (**p-tau217**) for discriminating early-onset Alzheimer's disease (**EOAD**) from early-onset non-AD (**EOnonAD**)
2. **Characterize cross-sectional relationships** between plasma **p-tau217** and amyloid PET (**Centiloid**; [^{18}F]Florbetaben) and tau PET (**cortical [^{18}F]Flortaucipir SUVR**)
3. **Compare biomarker associations** with baseline clinical severity and longitudinal progression; measured by Clinical Dementia Rating-Sum of Boxes (**CDR-SB**)

Background

Plasma p-tau217 is a scalable blood-based AD biomarker, but utility in the early-onset (age<65) group remains unclear

Amyloid and tau PET provide established in vivo measures, with tau PET more closely reflecting clinical severity and disease stage

With data from the **Longitudinal Early-onset Alzheimer's Disease Study (LEADS),** we examine how plasma p-tau217 relates to amyloid and tau PET, and to clinical severity and progression in EOAD

Methodology

Cohort

1. Baseline: 489 participants with non-missing p-tau217 data and clinical diagnosis of early-onset mild cognitive impairment/dementia due to likely AD, assigned based on [^{18}F]Florbetaben PET visual read to EOAD (376; PET+) or EOnonAD (113; PET-). PET/CDR data is with same visit year.

2. Longitudinal: 210 EOAD patients with ≥2 CDR-SB

Biomarker Data

Plasma p-tau217 measured using the Quanterix AlzPATH assay; log-transformed for analyses using linear models

Amyloid PET burden: Centiloids (CL) derived from [^{18}F]Florbetaben SUVR using whole cerebellum reference

Tau PET burden: cortical [^{18}F]Flortaucipir SUVR, using inferior cerebellum gray matter reference and the Desikan-Killiany atlas of FreeSurfer cortical segmentation

Statistical Analysis

Receiver Operating Characteristic (ROC) curve analysis to evaluate discrimination of EOAD from EOnonAD using plasma p-tau217 at baseline

Linear regression models (adjusted for age, sex, years of education) to assess cross-sectional associations between:
- p-tau217 vs. Centiloid and cortical [^{18}F]Flortaucipir SUVR
- Biomarkers vs. baseline CDR-SB

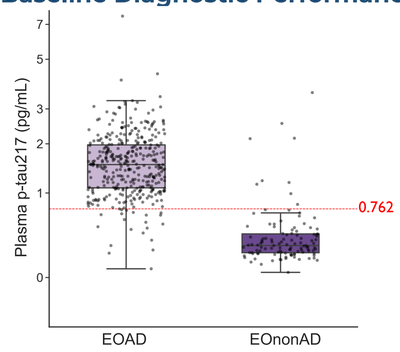
Linear mixed effects model (random intercept and slopes) to test associations between baseline biomarker and longitudinal change in CDR-SB. Standardized coefficients β are reported for all.

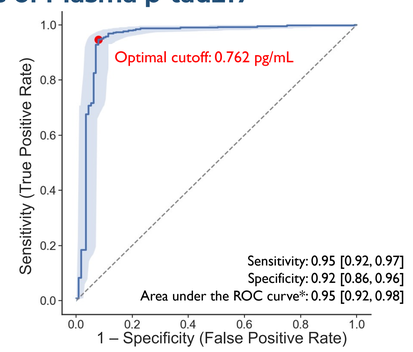
Results

Table 1 (Baseline)	N/A	Total (n = 489)	EOAD (A+) (n = 376)	EOnonAD (A-) (n = 113)	P-value
Sex - Female	0	248 (50.7)	202 (53.7)	46 (40.7)	*0.02*
Ethnicity – Hispanic/Latino	0	21 (4.3)	10 (2.7)	11 (9.7)	*0.003*
ApoE4 - Carriers	19	237 (48.5)	200 (53.2)	37 (32.7)	*<0.001*
Clinical Stage - Dementia	12	313 (64.0)	271 (72.1)	42 (37.2)	*<0.001*
Plasma p-tau217*	0	1.3 [0.7, 1.8]	1.5 [1.1, 2.0]	0.3 [0.2, 0.4]	*<0.001*
Centiloid	8	79.9 (48.9)	103.2 (27.6)	3.4 (10.0)	*<0.001*
Age	17	59.0 (4.6)	59.2 (4.0)	58.3 (6.3)	0.1
Education (years)	0	15.6 (2.5)	15.6 (2.4)	15.7 (2.7)	0.8
CDR-SB	18	3.6 (1.9)	3.9 (1.9)	2.6 (1.8)	*<0.001*
MMSE	13	22.4 (5.4)	21.2 (5.4)	26.0 (3.5)	*<0.001*
Cortical [^{18}F]Flortaucipir SUVR	17	1.7 (0.5)	1.9 (0.5)	1.1 (0.2)	*<0.001*

n (%) for categorical, mean (SD) for numeric values. *Median, Interquartile Range [Q1 Q3]. A: Amyloid PET Visual Read Status

Baseline Diagnostic Performance of Plasma p-tau217



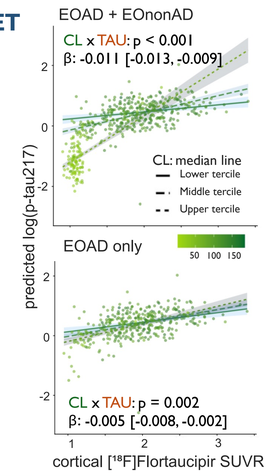


Associations with Amyloid PET and Tau PET

Model: log(p-tau217) ~ predictor(s) + covariates

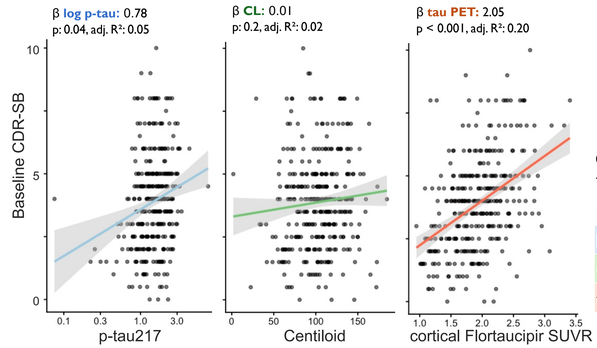
Predictor	CL, β 95% CI	TAU, β 95% CI	Adj. R^2
EOAD + EOnonAD (n = 468)			
CL	0.012 [0.011, 0.013]	NA	0.549
TAU	NA	1.100 [1.006, 1.195]	0.528
CL + TAU	0.007 [0.006, 0.009]	0.625 [0.512, 0.738]	0.64
CL * TAU	0.023 [0.019, 0.026,]	1.620 [1.421, 1.819]	*0.718*
EOAD (n = 357)			
CL	0.004 [0.003, 0.006]	NA	0.062
TAU*	NA	0.503 [0.409, 0.597]	0.237
CL + TAU*	0.002 [0.000, 0.003][a]	0.468 [0.369, 0.567]	0.243
CL * TAU*	0.010 [0.004, 0.016][b]	0.936 [0.612, 1.261]	*0.26*

CL: Centiloid. TAU: cortical [^{18}F]Flortaucipir SUVR. *Age is a significant covariate. Predictors in the table are all significant with p < 0.001 except for a: 0.04; b: 0.001.



Associations with Clinical Severity and Longitudinal Progression

Model: Baseline CDR-SB ~ individual biomarker + covariates



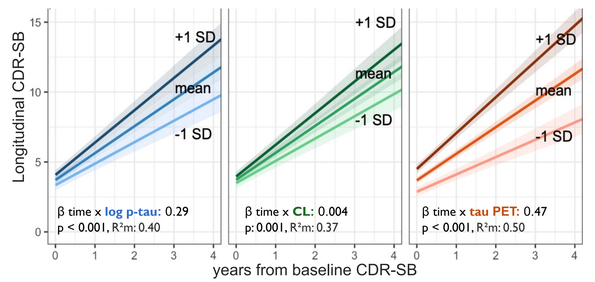
n = 346 EOAD

CDR-SB ~ all biomarkers + covariates

β biomarker, p-value	
log(p-tau217)	0.03, 0.9
Centiloid	-0.004, 0.2
tau $PET_{cortical}$	2.12, *<0.001*

adj R^2: 0.20

Model: CDR-SB ~ individual biomarker (baseline) x time to baseline + covariates + (1 + time | ID)



N = 733 records from n = 253 EOAD

CDR-SB ~ all biomarkers x time + covariates + (1 + time | ID)

β biomarker x time, p-value	
log(p-tau217)	0.04, 0.6
Centiloid	0.02, 0.5
Tau $PET_{cortical}$	0.14, *<0.001*

R^2_m: 0.50

Highlights

Plasma p-tau217 in early-onset participants with cognitive impairment:
- excellent baseline discrimination of EOAD from EOnonAD
- strong cross-sectional associations with tau PET; association with amyloid PET is stronger at lower tau levels and attenuated in EOAD
- weaker associations with clinical severity and progression than tau PET

Acknowledgements

Life Molecular Imaging and Avid Radiopharmaceuticals enabled the use of Florbetaben and Flortaucipir but did not provide direct funding and were not involved in data analysis or interpretation. Data collection and dissemination of the data presented in this manuscript were supported by the LEADS Consortium (R56/U01 AG057195, funded by the National Institute on Aging) as well as U24AG021886, Alzheimer's Association LEADS GENETICS-19-639372, Alzheimer's Association LDRFP-21-818464, Alzheimer's Association LDRFP-21-824473 and Alzheimer's Association LDRFP-21-828356.

Contact: marlene.lin@ucsf.edu