

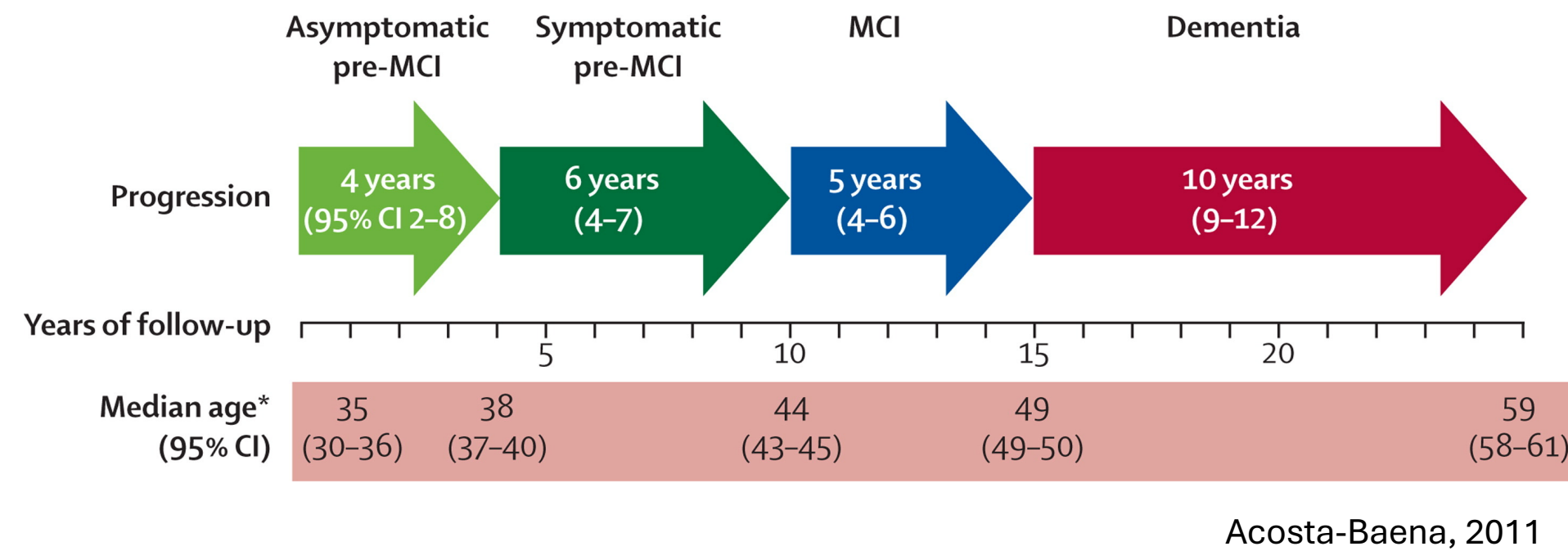
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Background

- Autosomal-dominant Alzheimer's disease (ADAD) caused by *PSEN1* mutations offers a model for studying the earliest biological changes in AD, given its highly predictable age at symptom onset.
- The Colombian *PSEN1* E280A kindred (Antioquia) includes ~6,000 relatives and ~1,400 confirmed mutation carriers, with median onset of 44 years for MCI and 49 years for dementia.



- Ultrasensitive plasma assays are now available and could reduce reliance on CSF and PET biomarkers, but their relationships with age in ADAD remain incompletely characterized.
- Plasma p-tau217 has shown the strongest diagnostic accuracy for AD pathology to date; Aβ42/Aβ40, GFAP, BD-tau, and NfL are other key candidate markers, each reflecting a distinct pathological process (amyloid accumulation, astrogliosis, brain-specific tau, and neuroaxonal injury, respectively).

Study aims

- Characterize age-related changes in plasma biomarkers among *PSEN1* E280A carriers and non-carriers.
- Examine associations between plasma biomarkers and cognitive performance (MMSE, CERAD Word List Delayed Recall) among carriers.
- Estimate the age at which each biomarker diverges between carriers and non-carriers.
- Compare each biomarker's ability to classify mutation carriers versus non-carriers.

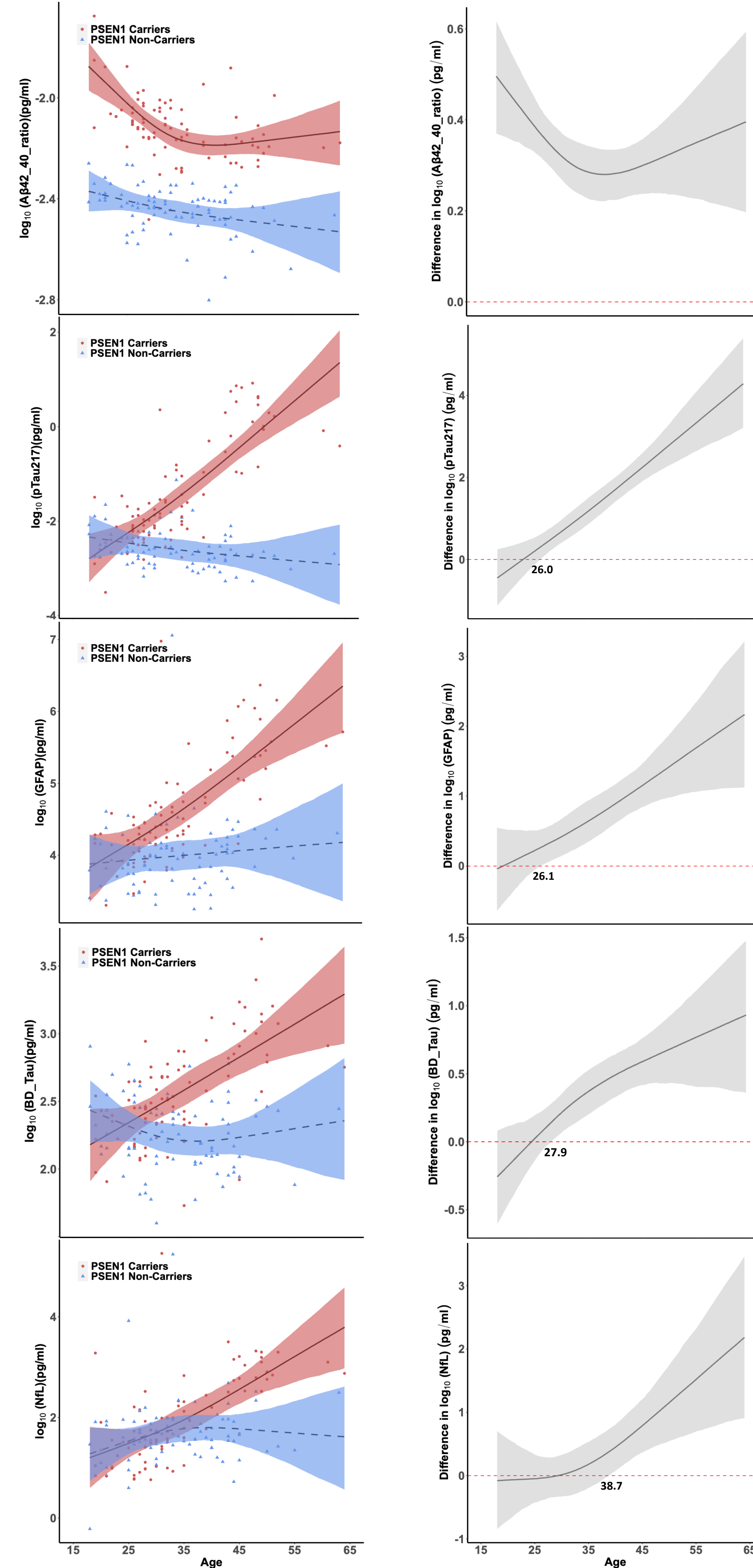
Methods

- Participants (ages 18–64) were recruited from the Colombian Alzheimer Prevention Initiative registry near the University of Antioquia (Medellín).
- Neuropsychological assessment included MMSE, Spanish CERAD Word List Delayed Recall, and FAST staging (≤ 2 indicating unimpaired status).
- Plasma p-tau217, Aβ42, and Aβ40 were measured using Lumipulse G1200 RUO (Fujirebio), and NfL, GFAP, and BD-tau using Simoa HDx (Neuro-4-plex D, Quanterix).
- Age-related biomarker trajectories were modeled using sex-adjusted linear regression and Bayesian restricted cubic splines to estimate divergence ages. Carrier discrimination was assessed using age- and sex-adjusted ROC analyses with DeLong's tests. Cognitive associations were tested using multiple regression adjusted for age, sex, and education, with backward AIC selection.

Plasma Biomarkers vs Age and Cognition

- In *PSEN1* E280A carriers, age was associated with lower Aβ42/Aβ40 and higher p-tau217, BD-tau, GFAP, and NfL, whereas in non-carriers only Aβ42/Aβ40 and p-tau217 showed age-related changes.
- Plasma p-tau217 was the strongest predictor of both MMSE and delayed recall, with only modest gains in explained variance from adding additional biomarkers ($\Delta R^2 \leq 0.076$). In individual models, GFAP showed the second strongest associations with cognition after p-tau217.

Divergence-Age Estimates Of Plasma Biomarkers

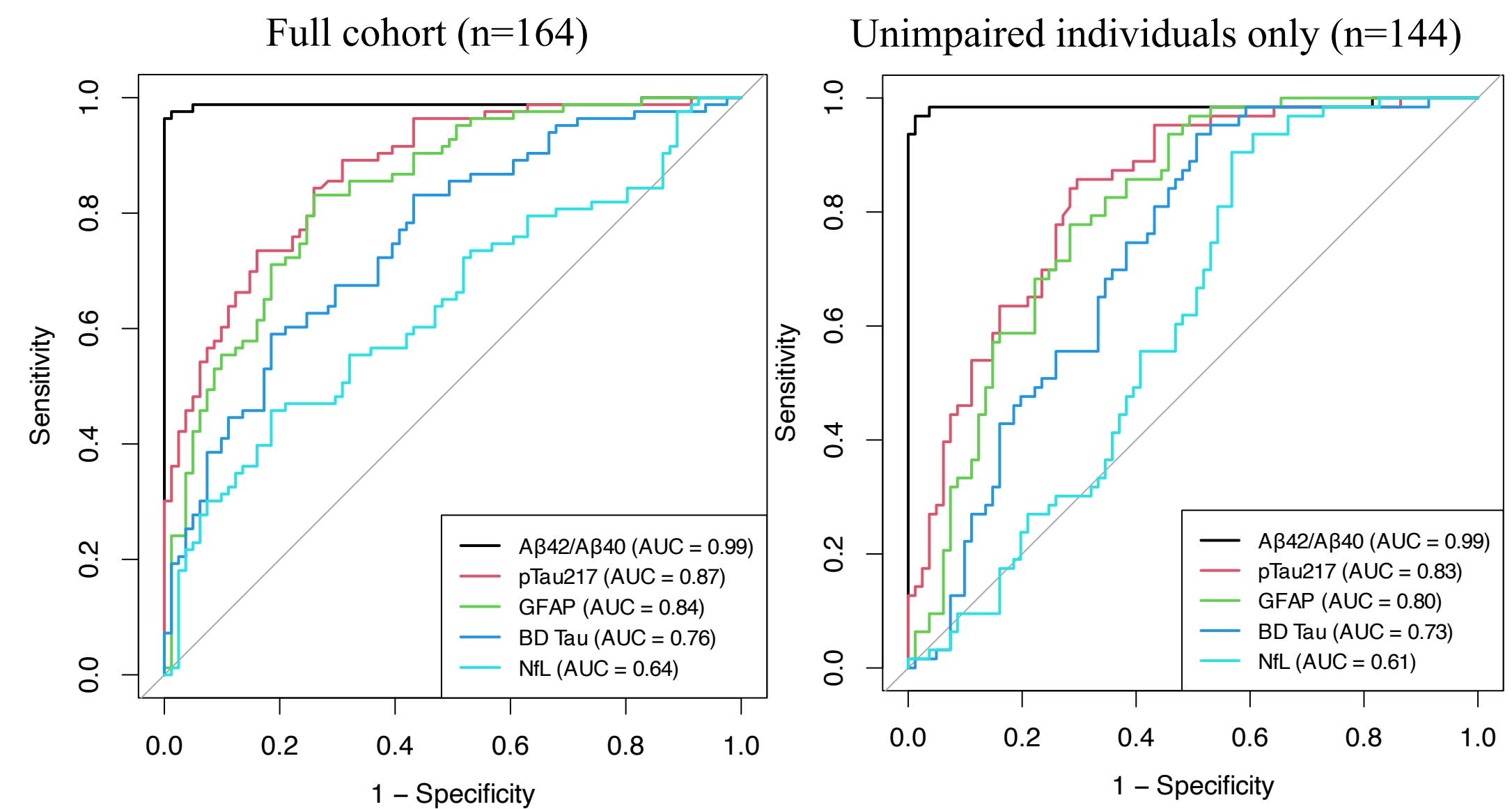


Left panel: Cross-sectional log-transformed plasma values of non-carriers and mutation carriers as a function of age. Right panel: Differences in log-transformed plasma values between carriers and non-carriers. Non-carrier levels are set at zero. The shaded areas represent 99% credibility intervals.

Sample Characteristics

	Carriers (n=83)	Non-carriers (n=81)	p value (Cohen's d)	Impaired Carriers (n=20)	Unimpaired Carriers (n=63)	p value (Cohen's d)
Age (years)	34.36±9.82	33.75±9.34	.758	48.60±5.65	29.84±5.63	3.71×10⁻¹¹
Sex (M/F)	38/45	39/42	.883	9/11	29/34	1
Education (years)	10.9±3.56	12.4±3.13	.006	8.9±3.61	11.5±3.33	.004
MMSE (/30)	25.98±5.04	28.77±1.27	6.44×10⁻⁰⁶ (-0.76)	18.85±5.64	28.24±1.49	6.05×10⁻¹¹ (-3.10)
CERAD Word List Delayed Recall	6.33±3.15	8.04±1.30	.001 (-0.71)	1.40±1.67	7.89±1.39	1.56×10⁻¹¹ (-4.44)
FAST	1.88±1.40	1.06±0.24	1.19×10⁻⁰⁶ (0.81)	4.15±0.93	1.16±0.37	5.73×10⁻¹⁵ (5.39)
Aβ42/Aβ40	0.12±0.02	0.09±0.01	4.07×10⁻²⁷ (2.61)	0.11±0.01	0.12±0.02	.001 (-0.64)
p-tau217 (pg/ml)	0.47±0.62	0.08±0.04	1.65×10⁻¹⁵ (0.87)	1.36±0.65	0.18±0.19	6.93×10⁻¹¹ (3.32)
BD-tau (pg/ml)	14.0±5.76	9.98±2.68	1.45×10⁻⁰⁷ (0.89)	20.8±6.83	11.9±3.16	1.15×10⁻⁰⁵ (2.07)
GFAP (pg/ml)	143.68±155.11	69.01±124.58	1.73×10⁻¹⁰ (0.53)	289.16±134.39	97.49±131.49	4.88×10⁻⁰⁹ (1.45)
NfL (pg/ml)	11.56±21.53	8.25±21.12	.019 (0.16)	19.83±6.78	8.93±23.87	4.30×10⁻⁰⁹ (0.52)

Group classification performances



Conclusion

- Plasma biomarkers exhibit a clear temporal cascade in *PSEN1* E280A ADAD: Aβ42/Aβ40 changes emerge earliest (childhood), followed sequentially by p-tau217, GFAP, BD-tau, and NfL.
- Plasma p-tau217, and to a lesser extent GFAP, show the strongest cross-sectional links to cognitive decline, supporting their use as sensitive markers for tracking disease progression and treatment response in *PSEN1* E280A carriers.

Reference

Acosta-Baena, Natalia, Diego Sepulveda-Falla, Carlos Mario Lopera-Gómez, et al. "Pre-Dementia Clinical Stages in Presenilin 1 E280A Familial Early-Onset Alzheimer's Disease: A Retrospective Cohort Study." *The Lancet Neurology* 10, no. 3 (2011): 213–20. [https://doi.org/10.1016/S1474-4422\(10\)70323-9](https://doi.org/10.1016/S1474-4422(10)70323-9).

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