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Original Article

Associations of plasma biomarkers with age in the presenilin-1 E280A autosomal dominant Alzheimer's disease kindred

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ABSTRACT

Background: Autosomal-dominant Alzheimer’s disease (ADAD) offers a model to define early biological changes in Alzheimer’s disease due to its predictable age at symptom onset. Although ultrasensitive plasma assays are available, their associations with age in ADAD remain incompletely characterized.

Objectives: To characterize age-related changes in plasma biomarkers and examine associations with cognition in *PSEN1* E280A ADAD.

Design and setting: Cross-sectional observational study in members of the Colombian *PSEN1* E280A kindred.

Participants: A total of 164 individuals were included, comprising 83 mutation carriers (mean age 34.36±9.82 years; 54% female) and 81 non-carriers (mean age 33.75±9.84 years; 52% female).

Measurements: Plasma Aβ42/Aβ40, phospho-tau217 (p-tau217), brain-derived tau (BD-tau), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) were quantified. Sex-adjusted associations with age, divergence ages between groups, classification performance (ROC curves), and associations with cognition (MMSE and CERAD delayed recall) were assessed.

Results: All plasma biomarkers were associated with age ($p < .01$). Divergence between carriers and non-carriers began with Aβ42/Aβ40 before age 18, followed by p-tau217 (26.0 years), GFAP (26.1 years), BD-tau (27.9 years), and NfL (38.7 years). Aβ42/Aβ40 showed the highest discrimination of mutation status (AUC=0.99), followed by p-tau217 (AUC=0.87) and GFAP (AUC=0.84). Among carriers, p-tau217, GFAP, BD-tau, and NfL were associated with MMSE, while p-tau217, GFAP, and NfL predicted CERAD delayed recall.

Conclusion: Plasma biomarkers exhibit a temporal cascade in *PSEN1* E280A ADAD. P-tau217 and GFAP show the strongest associations with early cognitive decline, suggesting their potential utility for tracking disease progression and monitoring treatment effects in E280A carriers.

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1. Introduction

Autosomal-dominant Alzheimer's disease (ADAD) due to *PSEN1* mutations provides a powerful model for characterizing the earliest biological changes of Alzheimer's disease (AD). The *PSEN1* E280A variant has been extensively studied in the large Colombian kindred from Antioquia, comprising ~6000 relatives, including ~1400 confirmed mutation carriers. In this population, the onset of clinical symptoms is remarkably consistent, with a median age at onset of 44 years (range 43–45) for mild cognitive impairment (MCI) and 49 years (range 49–50) for dementia [1]. This highly predictable disease course enables precise staging across the preclinical and symptomatic phases, offering an unparalleled opportunity to investigate the temporal unfolding of AD pathology.

Such a setting is especially advantageous for evaluating blood-based biomarkers, which constitute promising scalable tools to support clinical evaluation, trial selection, and disease monitoring. Their widespread implementation may substantially reduce the reliance on cerebrospinal fluid (CSF) biomarkers or positron emission tomography (PET) scans in specialized centers for AD diagnosis and lead to a more comprehensive assessment of cognitive impairment in settings in which advanced examinations are limited [2]. Among the most standard plasma biomarkers examined in the AD context, plasma tau phosphorylated at threonine 217 (p-tau217) has consistently demonstrated the greatest accuracy for detecting AD pathology [3–5]. Other key plasma biomarkers for AD include the Aβ42/Aβ40 ratio, an indicator of brain amyloid accumulation [6]; glial fibrillary acidic protein (GFAP), a marker of reactive astrogliosis [7]; brain-derived tau (BD-tau), which predominantly measures tau of brain rather than peripheral origin [8]; and neurofilament light (NfL), which reflects neuroaxonal injury [9].

Previous studies in this kindred have examined plasma biomarkers in isolation (e.g., Aβ42/Aβ40 [10–12], NfL [13–15], p-tau217 [16,17]) or in limited combinations within the same individuals, such as p-tau217 with NfL [18]; p-tau231, p-tau217, and NfL [19]; and Aβ42/Aβ40, p-tau181, NfL, and GFAP [20,21]. Among these, plasma Aβ42/Aβ40 most consistently distinguishes carriers from non-carriers [10–12], reflecting the lifelong Aβ42 overproduction driven by the *PSEN1* E280A mutation, and emerging decades before cognitive symptoms. Plasma p-tau217 has shown the highest diagnostic accuracy, outperforming plasma p-tau231 and NfL in differentiating carriers from non-carriers [19]. While baseline p-tau217 becomes abnormal earlier than p-tau231 or NfL, longitudinal changes in p-tau231 detect carriers sooner than changes in p-tau217 or NfL [19].

Although other prior studies in this kindred have examined sex differences in plasma biomarker trajectories [18], or focused on associations between physical activity and plasma biomarkers [20,21], none have simultaneously evaluated plasma Aβ42/Aβ40, p-tau217, BD-tau, GFAP, and NfL within the same individuals. Furthermore, BD-tau remains to be tested in the *PSEN1* E280A kindred, despite recent evidence suggesting that it is a sensitive marker of amyloidosis-related neurodegeneration [22].

This cross-sectional study provides the first integrated assessment of all five plasma biomarkers within the same *PSEN1* E280A individuals. By jointly examining associations with age, divergence-age estimates, classification performance, and cognitive outcomes, this study aims to clarify the temporal sequence of plasma biomarker changes in ADAD and to refine their comparative diagnostic and prognostic value across the disease continuum.

2. Methods

2.1. Participants

A total of 164 participants from the Colombian *PSEN1* E280A kindred were included in the study, comprising 83 *PSEN1* E280A carriers and 81 non-carriers, with ages ranging from 18 to 64 years. All participants were recruited from the Colombian Alzheimer Prevention Initiative (API) registry, which currently includes more than 5000 living members of the kindred descending from a common ancestor. Only individuals living near the metropolitan area surrounding the University of Antioquia, located in Medellín, Antioquia, Colombia, were invited to participate in the present study; of these, 14 had previously participated in the API ADAD clinical trial and were enrolled in the current observational study between 9 months and 4 years after completing the trial.

Among carriers, 63 were cognitively unimpaired, and 20 were cognitively impaired. Cognitive status was defined using the Functional Assessment Staging Test (FAST), a validated clinical staging instrument that tracks the sequential decline in a patient's ability to perform activities of daily living across seven stages [23], with scores ≤ 2 indicating unimpaired status. Exclusion criteria include the presence of a neurological, psychiatric, or systemic illness that might affect cognition or interfere with subsequent follow-up assessments.

2.2. Procedures

Clinical Ratings and Neuropsychological Tests: Clinical and cognitive assessments were undertaken at the University of Antioquia (Medellín, Colombia). Participants completed a clinical interview including the Mini-Mental State Examination (MMSE) [24], the Word List Delayed Recall from the Spanish CERAD battery [25], and the FAST [23]. Testing was conducted in Spanish by trained neuropsychologists or psychologists. Clinical histories and neurological examinations were performed by neurologists or physicians trained in the assessment of dementia. Clinical data were recorded using the clinical module of the Neurosciences Group of Antioquia's intranet.

Genotyping: Genomic DNA was extracted from blood following standard protocols. Characterization of the *PSEN1* E280A mutation was performed at the University of Antioquia using previously described methods [26].

Plasma biomarkers: Plasma samples were collected for each participant (non-fasting) at the University of Antioquia in 1 mL aliquots, predominantly in the morning (134; 81.7%) and less frequently in the afternoon (30; 18.3%), and stored at −80 °C until analysis. Concentrations of plasma p-tau217, Aβ42 and Aβ40 were measured using the Lumipulse *G*1200 RUO immunoassay (Fujirebio). NfL, GFAP and BD-tau were quantified using the Simoa HDx platform (Neuro-4-plex D, Quanterix) at the Michael T. Zuendel Family Biomarker Laboratory at Banner Sun Health Research Institute, as previously described. Signal variations within and between analytical runs were assessed using three internal quality control samples at the beginning and the end of each run. All available plasma samples and corresponding clinical data were included in the analyses.

2.3. Statistical analyses

Participants' Characteristics: We used chi-squared tests for categorical variables and independent-samples *t*-tests for continuous variables. When assumptions for parametric testing were not met, non-parametric Wilcoxon rank-sum tests were used. All p-values reported in the study are two-sided and unadjusted.

Associations between plasma biomarkers and age: Log-transformed plasma biomarker concentrations were modeled using linear regression. First, we examined age–biomarker associations in sex-adjusted models in the whole cohort and in *PSEN1* E280A carriers and non-carriers separately. To test whether these associations differed by *PSEN1* mutation status, we fitted a second model including an interaction between age and *PSEN1* status, adjusting for sex.

Divergence-age estimates of plasma biomarkers: We implemented methods previously reported in a study with a similar ADAD cohort [27]. In summary, we used a restricted cubic spline model to characterize the relationship between baseline plasma concentration and age. Model parameters were estimated with a Hamiltonian Markov

Chain Monte Carlo method, implemented in Stan (http://mc-stan.org). We specified weakly informative Cauchy prior distributions for the model parameters. Eight Markov chains were run with 10,000 iterations each, including 5000 warm-up iterations, with thinning set to 10, resulting in 4000 posterior samples. Convergence was assessed using the Gelman–Rubin diagnostic, which compares within-chain and between-chain variance, with values close to 1 indicating adequate convergence. This method allowed the estimation of both the median and 99% credible intervals (CrI) of the model fits across all ages for both carriers and non-carriers. It also allowed the estimation of the distribution of the differences in plasma concentrations between carriers and non-carriers with 99% CrIs. Based on the difference curve and its CrI, we subsequently estimated the age of onset as the earliest time point at which the 99% CrI of the distribution of differences did not overlap.

Group classification performances: Receiver operating characteristic (ROC) curves were generated using logistic models adjusted for age and sex, and the resulting area under the curve (AUC) values quantified each biomarker's ability to differentiate carriers from non-carriers. Differences in AUCs were formally compared using DeLong's test. For comparison with late-onset Alzheimer's disease, we additionally present ROC curves incorporating plasma p-tau217/Aβ42 ratio.

Associations between plasma biomarkers and cognitive performance: We used a two-step analytic approach to evaluate associations between plasma biomarkers and cognition in *PSEN1* E280A carriers. First, each biomarker (Aβ42/Aβ40, p-tau217, BD-tau, GFAP, and NfL) was entered independently into a multiple linear regression model, adjusted for age, sex, and education, to assess its individual association with cognitive performance. Second, to identify the combination of biomarkers that best explained cognitive variation, we fitted multivariable models that included all log-transformed biomarkers along with age, sex, and education. We then performed backward stepwise selection using the Akaike Information Criterion (AIC). At each step, we removed the predictor whose exclusion resulted in a lower (i.e., better) AIC value. This process continued until no further improvement in AIC was possible. The final models, therefore, included only the variables that improved overall model fit and contributed to explaining variance in cognitive outcomes. Finally, we compared the adjusted R^2 of the final models with those of models including only the biomarker with the strongest association to cognition to evaluate the added explanatory value. These procedures were conducted separately for MMSE and CERAD Word List Delayed Recall scores using the lm() and step() functions in R version 4.4.3.

3. Results

3.1. Participants' characteristics

Participant characteristics and baseline plasma biomarker concentrations are shown in Table 1 (left panel). Carriers and non-carriers were similar in age (34.36±9.82 vs. 33.75±9.34 years, p=.758) and sex distribution (38/45 vs. 39/42 male/female, p=.883). Carriers, however, had significantly fewer years of education (10.9 ± 3.56 vs. 12.4 ± 3.13, p=.006). As expected, *PSEN1* E280A carriers exhibited markedly higher plasma Aβ42/Aβ40 ratios ($p = 4.07\times10^{-27}$), as well as elevated p-tau217 ($p = 1.65\times10^{-15}$), BD-tau ($p = 1.45\times10^{-07}$), GFAP ($p = 1.73\times10^{-10}$), and NfL ($p = 6.44\times10^{-06}$) relative to non-carriers. Carriers also showed poorer cognitive performance on MMSE (25.98±5.04 vs. 28.77±1.27, $p = 6.44\times10^{-06}$), CERAD delayed recall (6.33±3.15 vs. 8.04±1.30, p=.001), and FAST (1.88±1.40 vs. 1.06±0.24, $p = 1.19\times10^{-06}$) compared to non-carriers. Unimpaired carriers had slightly lower MMSE scores compared to non-carriers (28.24±1.49 vs. 28.77±1.27, p=.023) but similar CERAD delayed recall (7.89±1.39 vs. 8.04±1.30, p=.550) and FAST scores (1.16±0.37 vs. 1.06±0.24, p=.060).

Characteristics of unimpaired and impaired carriers are presented in Table 1 (right panel). Impaired carriers were substantially older than unimpaired carriers (48.60±5.65 vs. 29.84±5.63 years, $p = 3.71\times10^{-11}$), had fewer years of education (8.9 ± 3.61 vs. 11.5 ± 3.33, p=.004), and demonstrated markedly reduced MMSE (18.85±5.64 vs. 28.24±1.49, $p = 6.05\times10^{-11}$) and CERAD word list delayed recall performance (1.40±1.67 vs. 7.89±1.39, $p = 1.56\times10^{-11}$). Impaired carriers also showed significantly lower concentrations of plasma Aβ42/Aβ40 (0.11±0.01 vs. 0.12±0.02, p=.001) and higher concentrations of p-tau217 (1.36±0.65 vs. 0.18±0.19, $p = 6.93\times10^{-11}$), BD-tau (20.8 ± 6.83 vs. 11.9 ± 3.16, $p = 1.15\times10^{-05}$), GFAP (289.16±134.39 vs. 97.49 ±131.49, $p = 4.88\times10^{-09}$), and NfL (19.83±6.78 vs. 8.93±23.87, $p = 4.30\times10^{-09}$). All p-values for comparisons of plasma biomarker levels presented in Table 1 remained significant (p<.05) after controlling the false discovery rate using the Benjamini–Hochberg procedure.

Table 1
Demographic, cognitive, and plasma biomarker characteristics of PSEN1 E280A mutation carriers and non-carriers.

	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)

3.2. Associations between plasma biomarkers and age

In sex-adjusted models, each plasma biomarker was significantly associated with age in the whole cohort (Aβ42/Aβ40: β=−0.004, *p*=.008; p-tau217: β=0.043, $p = 5.74\times10^{-8}$; BD-tau: β=0.012, $p = 5.24\times10^{-5}$; GFAP: β=0.034, $p = 6.72\times10^{-10}$; NfL: β=0.036, $p = 2.91\times10^{-9}$). This pattern was also observed in PSEN1 E280A carriers only (Aβ42/40: β=−0.006, $p = 2.34\times10^{-5}$; p-tau217: β=0.090, $p = 4.30\times10^{-19}$; BD-tau: β=0.025, $p = 4.13\times10^{-11}$; GFAP: β=0.055, $p = 7.22\times10^{-15}$; and NfL: β=0.055, $p = 6.17\times10^{-11}$) but not in non-carriers, in whom only Aβ42/Aβ40 (β=−0.004, $p = 5.02\times10^{-4}$) and p-tau217 (β=−0.014, *p*=.002) were modestly associated with age, but not BD-tau (β=−0.004, *p*=.207), GFAP (β=0.007, *p*=.217), or NfL (β=0.012, *p*=.113). Finally, sex-adjusted age×*PSEN1* status interactions were significant for all biomarkers (*p*<.001) except Aβ42/Aβ40 (*p*=.186), indicating higher age-related increase of plasma concentrations in mutation carriers compared to non-carriers. We found no significant age × sex interaction for any plasma biomarker (all *p*>.05), indicating similar age-related trajectories in males and females. However, after adjusting for age, females had a significantly higher Aβ42/Aβ40 ratio compared to males (β=0.06, *p*=.03). No significant sex differences were observed for the other plasma biomarkers. Sensitivity analyses using non-linear models (restricted cubic splines) yielded slightly lower mean squared errors than the corresponding linear models, although the differences were small, indicating that the linear models adequately captured the associations between plasma biomarker levels and age.

3.3. Divergence-age estimates of plasma biomarkers

To directly compare the association of each plasma biomarker with age, z-score curves of log-transformed plasma biomarker levels were rescaled to a minimum-maximum normalization (0–1), with higher values representing greater abnormalities in the mutation carriers (Fig. 1; individual plots from which the ages at significant difference were drawn are available in Supplementary Figure S2). Plasma Aβ42/Aβ40 levels were already higher in carriers at the youngest ages included in our sample (<18 years). Among the remaining plasma biomarkers, divergence between carriers and non-carriers occurred sequentially: p-tau217 at an estimated age of 26.0 years, GFAP at 26.1 years, BD-tau at 27.9 years, and NfL at 38.7 years. Carriers and non-carriers diverged on CERAD Word List Delayed Recall at 34.1 years.

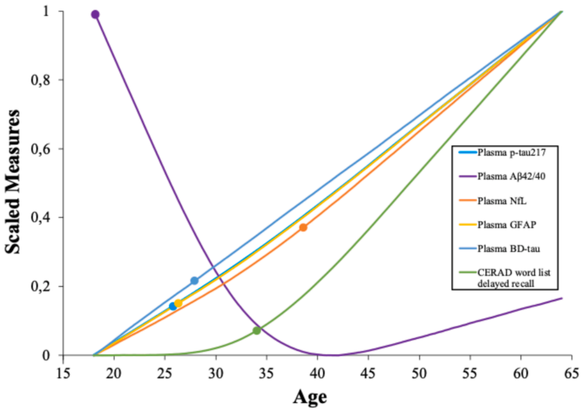

Fig. 1. Age and biomarker associations and comparison of age at onset of biomarker changes. Shown are mutation carrier standardized z-score curves scaled from zero to one for log-transformed plasma Aβ42/40, p-tau217, GFAP, BD-tau, NfL, and memory (CERAD word list delayed recall). CERAD word list delayed recall values were inverted using a 1 − scaled value transformation so that higher values indicate greater abnormality (i.e., poorer performance) relative to non-carriers. The age at significant difference from non-carriers is marked with a circle for each respective biomarker.

3.4. Group classification performances

Among the biomarkers, plasma Aβ42/Aβ40 was strongly associated with *PSEN1* E280A carriership (AUC=0.99; 95% Confidence Interval [CI], 0.97–1.00) followed by plasma p-tau217 (0.87; 95% CI, 0.82–0.92), plasma GFAP (0.84; 95% CI, 0.78–0.90), plasma BD-tau (0.76; 95% CI, 0.68–0.83) and plasma NfL (0.64; 95% CI, 0.55–0.72), as shown in Fig. 2A. Pairwise comparison of AUCs using DeLong's test revealed significant differences among several plasma biomarkers. Aβ42/Aβ40 showed significantly higher discriminative performance than all other markers (all *p*<.001). P-tau217 also outperformed NfL (*p*<.001) and BD-tau (*p*=.002) but did not differ significantly from GFAP (*p*=.259). GFAP demonstrated greater accuracy than BD-tau (*p*=.034) and NfL (*p*<.001). Finally, BD-tau displayed higher accuracy compared to NfL (*p*=.014).

Among cognitively unimpaired participants only (81 non-carriers, 63 carriers), plasma Aβ42/Aβ40 again showed the strongest discrimination between *PSEN1* E280A carriers and non-carriers (AUC=0.99; 95% CI, 0.96–1.00), followed by p-tau217 (AUC=0.83; 95% CI, 0.76–0.90), GFAP (AUC=0.80; 95% CI, 0.73–0.87), BD-tau (AUC=0.73; 95% CI, 0.64–0.81), and NfL (AUC=0.61; 95% CI, 0.52–0.70) as shown in Fig. 2B Pairwise comparison of AUCs using DeLong's test revealed significant differences among several plasma biomarkers in the unimpaired subgroup. Aβ42/Aβ40 showed significantly higher discriminative performance than all other markers (vs. p-tau217, GFAP, BD-tau, and NfL; all *p*<.001). P-tau217 also outperformed NfL (*p*<.001) and BD-tau (*p*=.012) but did not differ significantly from GFAP (*p*=.405). GFAP and BD-tau both demonstrated greater accuracy than NfL (*p*<.001 and *p*=.006, respectively), whereas GFAP and BD-tau did not differ significantly from each other (*p*=.075).

In supplementary analyses, plasma p-tau217/Aβ42 showed lower discriminative accuracy than plasma Aβ42/Aβ40 and p-tau217 (*p*<.001), comparable performance to GFAP and BD-tau (*p*>.05), and higher accuracy than NfL (*p*=.001) in the full sample. Among cognitively unimpaired individuals, p-tau217/Aβ42 performed worse than Aβ42/Aβ40, p-tau217, and GFAP (all *p*<.05), showed similar accuracy to BD-tau (*p*>.05), and outperformed NfL (*p*=.01). ROC curves are shown in supplementary Figure S1.

Finally, ROC analyses indicated that plasma p-tau217 is a highly robust predictor of clinical status in *PSEN1* E280A carriers (AUC = 0.987; $p = 6.76\times10^{-5}$). Comparing 20 impaired and 63 unimpaired carriers, an optimal cutoff of 0.384 achieved perfect sensitivity (1.0) and high specificity (0.937).

3.5. Associations between plasma biomarkers and cognition

In *PSEN1* E280A carriers, several plasma biomarkers showed significant associations with global cognition after adjustment for age, sex, and education. Among them, p-tau217 demonstrated the strongest relationship with MMSE performance (β=−3.55, $p = 6.76\times10^{-10}$), followed by GFAP (β=−3.26, $p = 3.16\times10^{-05}$), BD-tau (β=−5.91, $p = 8.19\times10^{-05}$), and NfL (β=−2.20, $p = 5.21\times10^{-04}$), all of which were significantly associated with poorer cognitive performance. In contrast, plasma Aβ42/Aβ40 showed no significant association with MMSE (β=−6.44, *p*=.076). A similar pattern was observed for delayed recall. Plasma p-tau217 again showed the strongest association (β=−1.58, $p = 5.61\times10^{-07}$), followed by GFAP (β=−1.46, $p = 5.35\times10^{-04}$) and NfL (β=−1.10, *p*=.001). BD-tau was associated with delayed recall in unadjusted analyses (β=−5.19, $p = 9.35\times10^{-10}$), but this effect was no longer significant after controlling for age, sex, and education (β=−1.12, *p*=.176), nor was Aβ42/Aβ40 (β=−3.31, *p*=.085). In non-carriers, none of the plasma biomarkers were associated with either MMSE performance or delayed recall (all *p*>.05).

To identify the plasma biomarkers most strongly associated with global cognition among *PSEN1* E280A carriers, we performed backward stepwise selection starting from a full multivariable model including all

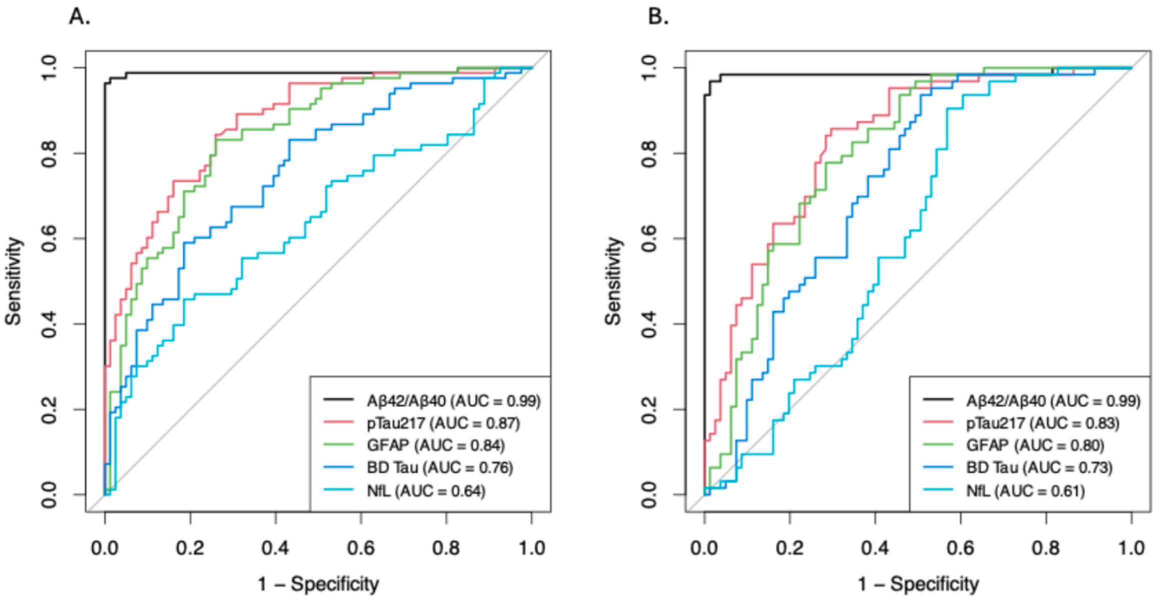

Fig. 2. Group classification performances. Receiver operating characteristic (ROC) curves providing AUCs for the discrimination between carriers and non-carriers are shown for each log-transformed plasma biomarker (Aβ42/Aβ40, p-tau217, GFAP, BD-tau, and NfL), based on logistic regression models adjusted for age and sex. Panel A shows ROC curves for the full sample of impaired and unimpaired participants ($n = 164$), and Panel B shows ROC curves for unimpaired individuals only ($n = 144$).

log-transformed biomarkers (Aβ42/Aβ40, p-tau217, BD-tau, GFAP, and NfL) and demographic covariates (age, sex, education). The optimal model for predicting MMSE scores retained p-tau217 and Aβ42/Aβ40 as biomarker predictors. P-tau217 emerged as the strongest correlate of MMSE scores ($\beta=-4.04$, $p = 8.51\times10^{-22}$), and Aβ42/Aβ40 contributed more modestly ($\beta=-6.81$, $p=.01$). No additional plasma biomarkers (GFAP, BD-tau, NfL) improved model fit once p-tau217 was included, and demographic covariates did not remain in the final model. The final model achieved an adjusted $R^2=0.688$, which constituted only a minimal increase relative to the p-tau217-only model (adjusted $R^2=0.665$). For delayed recall, the backward AIC procedure retained p-tau217, Aβ42/Aβ40, BD-tau, and the covariates age, sex, and education. Among biomarkers, p-tau217 was the strongest predictor of poorer delayed recall performance ($\beta=–2.03$, $p = 3.84\times10^{-8}$). Aβ42/Aβ40 and BD-tau were also significant predictors ($\beta=–4.40$, $p=.007$; $\beta=1.74$, $p=.034$, respectively). Among covariates, older age ($\beta=–0.11$, $p = 8.30\times10^{-4}$) and lower educational attainment ($\beta=0.17$, $p=.004$) were significantly associated with poorer scores. Female sex showed a nonsignificant trend toward lower performance compared to males ($\beta=–0.63$, $p=.099$). The final model achieved an adjusted $R^2=0.737$, compared to 0.661 for the model including only plasma p-tau217.

4. Discussion

This work presents the first comparative study of plasma biomarkers, including Aβ42/Aβ40, p-tau217, BD-tau, GFAP, and NfL in *PSEN1* E280A carriers, providing a comprehensive characterization of their age-related trajectories across the preclinical and symptomatic phases of ADAD.

Although all plasma biomarkers were associated with age in both the entire cohort and among *PSEN1* E280A carriers only, their divergence from normal levels occurred in a clear temporal order: Aβ42/Aβ40 (<18 years), p-tau217 (26.0 years), GFAP (26.1 years), BD-tau (27.9 years), and NfL (38.7 years). Plasma Aβ42/Aβ40 showed the strongest classification performance (AUC=0.99), followed by p-tau217 (AUC=0.87), GFAP (AUC=0.84), BD-tau (AUC=0.76) and NfL (AUC=0.64). Restricting analyses to cognitively unimpaired carriers produced the same ranking, with only small reductions in overall accuracy. Finally, in cross-sectional analyses that included each plasma biomarker individually and adjusted for age, sex, and education, p-tau217 emerged as the biomarker most strongly associated with MMSE and CERAD word list delayed recall, followed by GFAP and BD-tau/NfL. Accounting for model complexity, final backward AIC-selected models yielded only a marginal to small increase in explained cognitive variance.

The very early divergence and high discriminatory power of plasma Aβ42/Aβ40 are consistent with the pathophysiology of *PSEN1* E280A, a mutation that leads to lifelong Aβ42 overproduction beginning in childhood (ages 9–17) [10] and continuing throughout adulthood [11, 12]. The increased Aβ42/Aβ40 ratios observed in *PSEN1* E280A carriers, reflecting overproduction of the Aβ42 peptide, contrast with the decreased plasma Aβ42/Aβ40 ratios seen in the course of sporadic AD, which have been associated with cross-sectional and longitudinal amyloid plaque burden measured by PET [6]. Elevated levels of plasma Aβ42 in PSEN1 E280A carriers limits the relevance of the p-tau217/Aβ42 ratio in this ADAD subtype, although this ratio performs well diagnostically in sporadic AD [28]. Plasma p-tau217 and GFAP diverged at nearly identical ages, with p-tau217 showing substantially stronger associations with both MMSE and CERAD word list delayed recall. The divergence-age estimate obtained for plasma p-tau217 is consistent with a previous analysis in this cohort, which reported a divergence age of 25.9 years [19]. Although observational, the early abnormality observed for GFAP reinforces emerging evidence that astrocytic reactivity, as indexed peripherally by plasma GFAP [7], represents an early inflection point in tau-related processes consistent with previous work showing that increased GFAP levels are associated with the amplification of tau pathology in Aβ-positive clinically normal individuals without *PSEN1* E280A mutation [29]. This early glial contribution to tau amplification aligns with results from a recent PET study, which reported the colocalization of tau pathology and inflammation in the brains of individuals with MCI due to early-onset AD [30]. More broadly, inflammatory processes are increasingly understood as major cellular drivers and regulators of tau pathology [31,32]. GFAP therefore represents a non-specific but important biomarker of AD pathogenesis [33,34].

While plasma Aβ42/Aβ40 diverges as early as childhood in E280A carriers [10–12], CSF Aβ42 declines around age 24 [11], and fibrillar Aβ plaques detected by Aβ-PET accumulate later in the disease course, typically in the mid to late twenties [35]. This temporal proximity to the observed age of plasma GFAP divergence is consistent with the view that GFAP serves as an early AD marker associated with the emergence of fibrillar Aβ plaques [36]. In a previous study on a Swedish population with ADAD, plasma GFAP showed the earliest increase, approximately 10 years before estimated symptom onset, followed by increases in p-tau181 (∼6 years) and NfL (∼2 years), occuring closer to the expected onset [37]. In Down syndrome, plasma GFAP has been reported to diverge after Aβ-PET and plasma p-tau217 but before tau-PET, and to partially mediate the association between Aβ-PET and plasma p-tau217 (42.1%) and, to a lesser extent, between Aβ-PET and tau-PET (15.3%) [38]. However, the relationship between Aβ-PET signal and plasma GFAP–defined astrocyte reactivity is modulated by the presence of microglial activation, as indicated by a positive TSPO-PET scan [39]. In the absence of microglial activation, Aβ-burden has been associated with higher plasma p-tau217 and tau-PET signal but not with astrocyte reactivity or cognitive decline. When microglial activation was present, however, Aβ-burden, astrocyte reactivity, tau pathology, and cognition were all interrelated [39]. Activated microglia could not be assessed in the present study. Further research is needed to determine whether microglial activation causally drives Aβ-related astrocyte reactivity and to elucidate the exact mechanisms underlying this response. Overall, our findings support plasma GFAP as a biomarker of non-specific pathophysiological processes associated with Alzheimer's disease, consistent with the 2024 Alzheimer's Association criteria for AD diagnosis and staging [40] and complementary to the amyloid–tau–neurodegeneration (A/T/N) framework [41].

Model selection analyses revealed that shared explained variance by p-tau217 and GFAP reduced the incremental value of GFAP in multivariable models predicting cognition. Aβ42/Aβ40, despite its very early divergence, was not independently associated with cognition. In the final AIC-optimized models, p-tau217 and Aβ42/Aβ40 jointly predicted MMSE, while delayed recall also retained BD-tau and demographic factors. The positive association observed for BD-tau in the final model should be interpreted cautiously and may reflect a statistical suppression effect arising from the inclusion of correlated biomarkers and covariates. The inclusion of Aβ42/Aβ40 yielded only a marginal improvement in MMSE model fit (adjusted R^2=0.665 versus 0.688), whereas delayed recall benefited more substantially from additional predictors (adjusted R^2=0.661 versus 0.737). Overall, these findings underscore the dominant role of p-tau217 as the primary cross-sectional correlate of cognition in ADAD, with other variables contributing smaller, complementary effects.

Accordingly, integrating plasma p-tau217 with tau-PET in a sequential workflow may improve staging precision and risk stratification in AD [42]. Ultimately, refined plasma biomarker panels could support blood-based screening, monitoring, and therapeutic targeting.

5. Limitations

Strengths of this study include the uniquely well-characterized *PSEN1* E280A cohort, the use of ultrasensitive plasma assays, and the integration of complementary analytical frameworks (associations with age, divergence-age modeling, AUCs, and cognition–biomarker associations). Although samples were collected under non-fasting conditions, available evidence suggests minimal impact of fasting status on the biomarkers examined [43].

Several limitations also warrant consideration. First, the sample was restricted to individuals enrolled in the API registry residing near the University of Antioquia in Medellín, Antioquia, Colombia. Second, 14 participants had previously been enrolled in the API ADAD clinical trial and were recruited in the current observational study between 9 months and 4 years after completing the trial. Third, Aβ42/Aβ40 alterations are mutation-specific, limiting generalization to sporadic AD or other ADAD mutations. Fourth, cross-sectional analyses cannot establish temporal predictive utility, and longitudinal studies will be needed to determine the predictive value of plasma biomarkers for clinical conversion. Fifth, the inclusion of additional cognitive domains (e.g., executive function and language) would have allowed for a more comprehensive characterization of the relationship between plasma biomarkers and cognitive performance.

We also observed a small but statistically significant negative association between age and plasma p-tau217 levels in PSEN1 E280A non-carriers. Although this finding should be interpreted cautiously, future studies examining plasma p-tau217 levels earlier in life may help to better characterize its distribution across the lifespan, building on recent work reporting higher plasma p-tau217 concentrations in newborns compared with older individuals and patients with Alzheimer's disease [44]. Finally, although our cohort is the world's largest known ADAD kindred, greater sampling density would further refine divergence-age estimates.

6. Conclusions

These results delineate a clear temporal cascade of plasma biomarker changes in *PSEN1* E280A autosomal-dominant Alzheimer's disease, beginning with changes in plasma Aβ42/Aβ40, followed by p-tau217, GFAP, BD-tau, and NfL. Plasma p-tau217, and to a lesser degree GFAP, show the strongest links to emerging cognitive decline, suggesting their potential utility as sensitive biomarkers for monitoring disease progression and therapeutic response in clinical trials targeting *PSEN1* E280A carriers.

Glossary

Aβ: Amyloid-β
AD: Alzheimer's disease
ADAD: Autosomal-dominant Alzheimer's disease
AUC: Area under the curve
BD-tau: Brain-derived tau
CERAD: Consortium to Establish a Registry for Alzheimer's disease
CI: Confidence Interval
CSF: Cerebrospinal Fluid
FAST: Functional assessment staging tool
GFAP: Glial fibrillary acidic protein
MCI: Mild Cognitive Impairment
MMSE: Mini-Mental State Examination
MRI: Magnetic resonance imaging
NfL: Neurofilament Light
P-tau217: Phosphorylated-tau at threonine 217
PET: Positron emission tomography
PSEN1: Presenilin-1 gene
ROC: Receiver operating characteristic

Declaration of generative AI and AI-assisted technologies in the writing process

I have not used any AI at all.

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Ethics approval and consent to participate

All participants provided written informed consent before participating and were compensated. The study was approved by the University of Antioquia (Medellin, Colombia) local institutional review boards, and in alignment with international Institutional Review Board (IRB) standards. Researchers and participants were blind to genetic status.

Data of availability

Anonymized clinical and genetic data are available upon request, subject to an internal review by Dr. Quiroz to ensure that the participants' anonymity, confidentiality, and *PSEN1* E280A carrier or non-carrier status are protected. Data requests will be considered based on a proposal review and completion of a data sharing agreement, in accordance with the University of Antioquia and Mass General Brigham institutional guidelines. Please submit data requests to the corresponding author.

CRediT authorship contribution statement

Vincent Malotaux: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Vivian Ku:** Writing – review & editing, Formal analysis, Conceptualization. **Paula Ospina Lopera:** Writing – review & editing, Investigation. **Yi Su:** Writing – review & editing, Visualization, Formal analysis. **Yinghua Chen:** Writing – review & editing, Visualization, Formal analysis. **Alpana Singh:** Writing – review & editing. **Jonathan Ruiz-Triviño:** Writing – review & editing, Investigation. **María José Hidalgo:** Writing – review & editing, Investigation. **Laura Osorio:** Writing – review & editing, Investigation. **Laura Serna:** Writing – review & editing, Investigation. **Daniela Giraldo:** Writing – review & editing, Investigation. **Diana Alzate:** Writing – review & editing, Investigation. **Bing He:** Writing – review & editing. **Catarina Tristão-Pereira:** Writing – review & editing. **Liliana Ramirez Gomez:** Writing – review & editing. **Sonia Do Carmo:** Writing – review & editing. **A. Claudio Cuello:** Writing – review & editing. **Nicholas J. Ashton:** Writing – review & editing. **Eric M. Reiman:** Writing – review & editing. **David Aguillón:** Writing – review & editing, Investigation. **Yakeel T. Quiroz:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Quiroz reports a relationship with Biogen Inc that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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