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RESEARCH ARTICLE

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Prognostic value of plasma %p-tau217 in cognitively unimpaired older adults

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Abstract

INTRODUCTION: We evaluated the prognostic value of baseline plasma phosphorylated tau 217 ratio (%p-tau217) for predicting long-term progression in cognitively unimpaired (CU) older adults.

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METHODS: We analyzed 982 community-dwelling individuals followed annually for up to 12 years. Baseline %p-tau217 levels were quantified by mass spectrometry and stratified into four strata using previously defined cut-offs. Outcomes included longitudinal changes in cognition, neurodegeneration, and progression to mild cognitive impairment (MCI)/dementia. Results were replicated with immunoassays in the same and an independent primary care cohort ($n = 1204$).

RESULTS: Participants with Elevated/High %p-tau217 exhibited accelerated cognitive decline, hippocampal atrophy, and significantly higher risks of progression to MCI (hazard ratio [HR] > 6.0) and dementia (HR > 9.9). The Low group demonstrated a 92.2% 10-year negative predictive value for any progression.

DISCUSSION: Our results suggest that %p-tau217 is a robust prognostic biomarker, accurately distinguishing CU individuals at minimal risk from those at high risk of future AD-related clinical and neurodegenerative decline. Similar performance was achieved by immunoassays.

KEYWORDS
amyloid, biomarkers, MCI, plasma, preclinical Alzheimer's disease

Highlights

- ~1000 unimpaired community individuals were followed for up to 12 years.
- Baseline %p-tau217 predicted cognitive decline, accelerated neurodegeneration, and future progression to MCI/dementia.
- Low p-tau217 had very high negative predictive value (> 90%) to rule out future decline.
- %p-tau217 outperformed p-tau217 immunoassays in stratifying high-risk groups.

1 | BACKGROUND

Alzheimer's disease (AD) accounts for 60% to 80% of diagnosed dementias worldwide. Early detection and intervention are crucial yet challenging, as amyloid beta (Aβ) deposition and tau aggregation in the brain can precede the onset of overt cognitive impairment by years or even decades.[1] The recent approval of disease-modifying drugs targeting Aβ plaques has intensified the necessity for accurate, cost-effective, and accessible biomarkers to identify AD in its preclinical phase,[1–3] particularly as emerging clinical trials increasingly focus on asymptomatic or genetically at-risk individuals to evaluate whether therapeutic intervention earlier in life can delay or even prevent the onset of cognitive decline.[3–5]

Blood-based biomarkers, especially those of phosphorylated tau species,[6] have shown great promise for detecting underlying AD pathology and predicting disease progression.[7] Among them, phosphorylated tau at threonine 217 (p-tau217) has emerged as a particularly promising biomarker candidate,[8] closely correlating with in vivo Aβ and tau burden in positron emission tomography (PET) and cerebrospinal fluid (CSF),[9,10] as well as with longitudinal cognitive decline.[11] Liquid chromatography–tandem mass spectrometry (LC-MS/MS) also enables quantification of non-phosphorylated tau at threonine 217 (np-tau217), and the ratio of p-tau217 to np-tau217 (expressed as %p-tau217) has been proposed as a potentially more precise metric compared to p-tau217.[12] By normalizing against the non-phosphorylated peptide, the %p-tau217 ratio mitigates against physiological confounders such as chronic kidney disease and inter-individual differences in protein metabolism,[13] enhancing the performance of plasma biomarkers to a level clinically equivalent to established CSF measurements.[14,15]

Previous investigations documented promising associations between plasma p-tau217 concentrations and future cognitive decline among CU individuals.[10,14,16–18] Nevertheless, many of these studies were constrained by relatively short study durations, infrequent assessments, or small sample sizes. In addition, several relied on clinical trial or memory-clinic populations, which may restrict the generalization of their findings. Consequently, more community-based data are needed to more rigorously establish the utility of p-tau217 for real-world population risk stratification.[18] Moreover, evidence regarding %p-tau217 remains scarce due to its relatively recent introduction.[14]

Finally, the association between p-tau217 and AD-related neurodegeneration is still insufficiently characterized.[19] Clarifying this link is essential, as neurodegeneration is a core pathophysiological hallmark of the disease and closely correlates with clinical progression.[1] Here, we leveraged data from a large, single-center cohort of older CU individuals, with up to 12 years of annual follow-ups, to assess the prognostic value of baseline plasma %p-tau217 for long-term clinical progression, cognitive decline, and neurodegeneration in this population. Findings were replicated using immunoassay-based p-tau217 in the same and in a primary care cohort, another important target population for future screening.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed from inception through July 7, 2025, for studies investigating longitudinal outcomes associated with p-tau217 in cognitively unimpaired individuals. Several studies reported that elevated plasma p-tau217 levels were associated with tau and amyloid accumulation as assessed by PET and CSF. However, evidence remains limited regarding the capacity of plasma p-tau217 biomarkers to identify cognitively unimpaired individuals at substantial long-term risk of progression to MCI or dementia.
2. **Interpretation**: Elevated plasma %p-tau217 robustly associated with accelerated cognitive decline, increased risk of progression to MCI and dementia, and faster neurodegeneration. High negative predictive values (>90%) suggest that p-tau217 may be an excellent tool for identifying low-risk community individuals. Overall, our results support incorporating plasma p-tau217 testing into risk-stratification strategies for preclinical AD in both clinical practice and research.
3. **Future directions**: Future studies may validate our findings in more diverse populations, including younger individuals, different demographics, and diverse genetic backgrounds.

2 | METHODS

2.1 | Study participants

The Vallecas Project (VP) is a longitudinal, single-center, community-based study conducted in Madrid, Spain. This study enrolled 1173 older individuals (age range: 69 to 85 years; 64% female) who self-perceived as physically and cognitively healthy. Participants underwent annual clinical and neuropsychological assessment, blood extraction, and 3T magnetic resonance imaging (MRI), spanning a total of 12 years (2011 to 2023). Detailed inclusion and exclusion criteria are provided in Supplementary Methods 1.1. All participants provided written informed consent, and the VP was approved by the ethics committee of the Instituto de Salud Carlos III. For this study, we included individuals with sufficient plasma available for LC-MS/MS analysis at or within 2 years of their initial visit, which served as baseline for subsequent analyses, and whose CU status at that visit was confirmed using standardized criteria.

2.2 | Clinical and neuropsychological assessment

At each annual visit participants completed a semi-structured medical interview and a comprehensive neuropsychological assessment evaluating multiple cognitive domains, subjective cognitive decline (SCD), and functional impairment (Supplementary Methods 1.2.1). After each visit, a clinical diagnosis of CU, mild cognitive impairment (MCI), or dementia was assigned by consensus between the clinical and neuropsychological evaluators, based on standardized criteria (Supplementary Methods 1.2.2).

2.3 | Plasma biomarker measurements

Blood samples were collected annually and processed as detailed in Supplementary Materials 1.3.1. The plasma analyses were performed while all personnel analyzing the samples were blinded to all clinical or biomarker data. LC-MS/MS, performed by C2N Diagnostics, LLC (St. Louis, MO, USA), was used to quantify baseline plasma levels of p-tau217 (p-tau217$_{C2N}$), np-tau217 (np-tau217$_{C2N}$), and %p-tau217 (Supplementary Methods 1.3.2).[20]

Longitudinal plasma levels of glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) were quantified locally using the SIMOA platform (Quanterix, Billerica, MA, USA)[21] at up to three time points, selected to maximize follow-up coverage, for a subset of randomly selected subjects ($n = 487$ Supplementary Methods 1.3.3).

2.4 | MRI imaging

Three-dimensional T1-weighted MRI scans were acquired at each visit using a 3T MRI scanner (GE Signa HDxt, Wisconsin, USA). Serial measurements of hippocampal volume (HippVol) were derived using longitudinal volumetry as implemented within the Computational Anatomy Toolbox version 12.9.[22] Additional details are provided in Supplementary Materials 1.4.

2.5 | Outcomes

The primary outcomes of our study were as follows: (1) cognitive trajectories of participants with different levels of baseline %p-tau217, assessed using a modified version of the Preclinical Alzheimer's Cog-

nitive Composite Scale (mPACC, Supplementary Methods 1.2.3)[23] and the Mini-Mental State Examination (MMSE); (2) clinical outcomes associated with different levels of baseline %p-tau217, including (a) longitudinal trajectories of clinical and functional deterioration, assessed using the Clinical Dementia Rating Scale sum of boxes (CDR-SB) and the Functional Activities Questionnaire (FAQ), and (b) individual risks of clinical progression to MCI or dementia; and (3) trajectories of neurodegeneration and neuroinflammation markers, consisting of (a) medial temporal lobe atrophy as indicated by HippVol; (b) neuronal injury, as indicated by plasma NfL; and (c) astrocyte reactivity and damage, as measured by plasma GFAP.

2.6 | Statistical analysis

Statistical analyses were conducted using R version 4.4.2. Longitudinal trajectories of the outcome variables were modeled using generalized additive models (GAMs), with baseline %p-tau217 as the main predictor and with age at baseline, sex, years of education, and APOE ε4 carriership included as covariates. %p-tau217 was treated as a categorical variable based on a three cut-off classification: Low (<2.66%), Intermediate (2.66 to 4.90%), Elevated (4.90 to 7.40%), and High (≥7.40%), where 2.66% and 4.90% corresponded to previously derived optimal cut-offs for predicting amyloid and tau PET positivity, respectively,[24] while ≥7.40% served as a high-risk cut-off intended to capture individuals with higher likelihood of advanced tau pathology.[25] Importantly, the use of predefined, biologically informed thresholds rather than data-driven quantiles provides a more realistic approach for assessing the potential performance of %-ptau217 in real-world populations, where fixed decision boundaries are essential for interpretation and implementation. GAMs included a general non-linear smooth term to model the potential temporal non-linearity of the variable trajectory and a "by %p-tau217" interaction term accounting for differential temporal trajectories across the different %p-tau217 groups. Finally, subject-specific random intercepts and slopes were included. We report comparisons between groups at baseline, 5 years, and 10 years of follow-up. To quantify the proportion of variance in longitudinal trajectories uniquely attributable to plasma %p-tau217, we compared full and null population-average GAMs that differed only in the inclusion of %p-tau217 group, both as a main effect and as a group-specific time smooth. The variance contribution of the biomarker was estimated as the difference in deviance explained between models, expressed as a percentage. Additional details about the GAM analysis are provided in Supplementary Materials 3.1.

Hazard ratios (HRs) for the progression to MCI and/or dementia were estimated using interval-censored Cox regression models, including the same covariates as the GAM models. The positive predictive value (PPV) and negative predictive value (NPV) for predicting MCI/dementia progression of the different %p-tau217 cut-offs were estimated based on inverse probability of censoring weights (IPCW) at 5 and 10 years after baseline (Supplementary Materials 3.2). HRs, NPVs, and PPVs are reported together with 95% confidence intervals (CIs).

2.7 | Replication analyses

Complementary p-tau217 measurements for the VP were obtained locally using a chemiluminescent enzyme immunoassay available for the automated LUMIPULSE platform from Fujirebio (p-tau217$_{Fujirebio}$, Supplementary Methods 1.3.4) and used to replicate the main outcomes described earlier.

Additionally, we report data from 1204 CU participants enrolled in the German Study on Ageing, Cognition and Dementia (AgeCoDe), a prospective multicenter study involving primary care patients aged over 80 years and following a study protocol and follow-up schedule comparable to that of the VP. Plasma p-tau217 measurements were obtained using the SIMOA ALZPath immunoassay platform (p-tau217$_{ALZPath}$) and were used to replicate (1) trajectories of global cognition (based on a comparable global cognitive composite, mPACC*, and MMSE); (2) trajectories of clinical (CDR-SB) and functional decline, as measured by the Lawton and Brody Instrumental Activities of Daily Living scale (IADL), used as a proxy for FAQ; and (3) individual risks of clinical progression to MCI/dementia at 5 and 7.5 years. Methodological details of the AgeCoDe are provided in Supplementary Methods 2.

For replication analyses, participants were first stratified according to baseline p-tau217 using previously derived optimal cut-offs for detecting amyloid and tau PET positivity, respectively, for both p-tau217$_{Fujirebio}$ and p-tau217$_{ALZPath}$.[9,26] To match the three-cut-off strategy used for %p-tau217, an additional cut-off was applied to define a High group comprising the same percentile of individuals with the highest p-tau217$_{Fujirebio}$ (VP) or p-tau217$_{ALZPath}$ (AgeCoDe) values as the %p-tau217 High group.

3 | RESULTS

The study included 982 CU individuals, following exclusion of 49 participants who were classified as having MCI at baseline, 130 with insufficient plasma available for LC-MS/MS, and 12 whose LC-MS/MS results did not meet quality control criteria. Participants were categorized as Low (n = 674, 68.6%), Intermediate (n = 145, 14.8%), Elevated (n = 103, 10.5%), and High (n = 60, 6.1%). Baseline characteristics of the cohort stratified by %p-tau217 group are presented in Table 1. Figure S1 provides pairwise comparisons of the most relevant outcomes.

3.1 | Longitudinal trajectories of cognition across %p-tau217 groups

mPACC and MMSE trajectories significantly differed across all %p-tau217 groups (Figure 1A,B), with higher %p-tau217 levels linked to progressively steeper declines in both metrics (p < 0.001 for all smooth difference terms). The Low and Intermediate groups demonstrated minimal decline over the study duration (Δ_{mPACC} < 0.58 points), even displaying a mild initial practice effect indicated by increasing mPACC scores in early visits. The Elevated group did not differ from

TABLE 1 Baseline demographic and biomarker characteristics of participants in the Vallecas Project cohort, stratified by baseline %p-tau217 levels.

	Overall	Low %p-tau217	Intermediate %p-tau217	Elevated %p-tau217	High %p-tau217	Effect size
N (%)	982 (100)	674 (68.6)	145 (14.8)	103 (10.5)	60 (6.1)	–
Age (years), mean ± SD	74.7 ± 3.9	74.5 ± 3.7	74.9 ± 4.2	75.5 ± 4.1	75.9 ± 4.2	$\eta^2 = 0.01$
Female, *n* (%)	639 (65.1)	428 (63.5)	100 (69.0)	70 (68.0)	41 (68.3)	–
APOE ε4 carriers, *n* (%)	165 (16.8)	69 (10.2)	37 (25.5)	42 (40.8)	17 (28.3)	–
Education (years), mean ± SD	10.4 ± 5.8	10.4 ± 5.8	10.6 ± 6.0	10.1 ± 5.3	10.0 ± 5.8	$\eta^2 < 0.01$
SCD, *n* (%)	617 (62.9)	411 (61.0)	90 (62.1)	70 (68.0)	46 (76.7)	–
MMSE score, mean ± SD	28.6 ± 1.6	28.7 ± 1.5	28.6 ± 1.6	28.8 ± 1.5	28.0 ± 2.1	$\eta^2 = 0.01$
mPACC score, mean ± SD	0.0 ± 0.8	0.0 ± 0.8	0.0 ± 0.9	−0.2 ± 0.8	−0.5 ± 0.8	$\eta^2 = 0.03$
FAQ score, mean ± SD	0.4 ± 0.8	0.4 ± 0.8	0.4 ± 1.0	0.5 ± 0.9	0.9 ± 1.1	$\eta^2 = 0.02$
P-tau217$_{C2N}$ (pg/mL), mean ± SD	1.2 ± 1.2	0.7 ± 0.2	1.6 ± 0.7	2.6 ± 1.2	4.3 ± 1.6	$\eta^2 = 0.71$
Np-tau217 $_{C2N}$ (pg/mL), mean ± SD	42.7 ± 14.4	42.3 ± 15.5	43.3 ± 16.8	44.7 ± 17.8	42.1 ± 11.1	$\eta^2 < 0.01$
%p-tau217, mean ± SD	2.9 ± 2.5	1.7 ± 0.4	3.6 ± 0.7	5.9 ± 0.7	10.3 ± 3.1	–
P-tau217$_{Fujirebio}$ (pg/mL), mean ± SD	0.19 ± 0.52	0.15 ± 0.56	0.23 ± 0.56	0.27 ± 0.19	0.39 ± 0.19	$\eta^2 = 0.02$
GFAP (pg/mL), mean ± SD	170.3 ± 110.0	135.6 ± 75.9	204.8 ± 159.1	213.7 ± 78.8	263.3 ± 116.8	$\eta^2 = 0.16$
NfL (pg/mL), mean ± SD	13.8 ± 8.2	12.6 ± 8.0	14.8 ± 9.3	15.1 ± 6.2	17.0 ± 8.5	$\eta^2 = 0.03$
HippVol, n.u. × 10^3, mean ± SD	2.1 ± 0.3	2.1 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	1.9 ± 0.3	$\eta^2 = 0.02$
Follow-up duration (years), mean ± SD	7.9 ± 3.3	8.3 ± 3.2	8.1 ± 3.0	7.6 ± 3.5	6.3 ± 3.6	$\eta^2 = 0.02$
Number of follow-up visits, median (range)	7 (1-10)	7 (1-10)	7 (1-10)	7 (1-10)	5 (1 - 9)	$\eta^2 = 0.08$

Note: The right column provides eta-squared (η^2) as an effect size estimator.
Abbreviations: *N*, *n*, number of subjects; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; np-tau217, non-phosphorylated tau217; p-tau217, tau phosphorylated at threonine 217; %p-tau217, ratio of p-tau217 to np-tau217; SCD, subjective cognitive decline; SD, standard deviation; HippVol, hippocampal volume normalized by total intracranial volume.

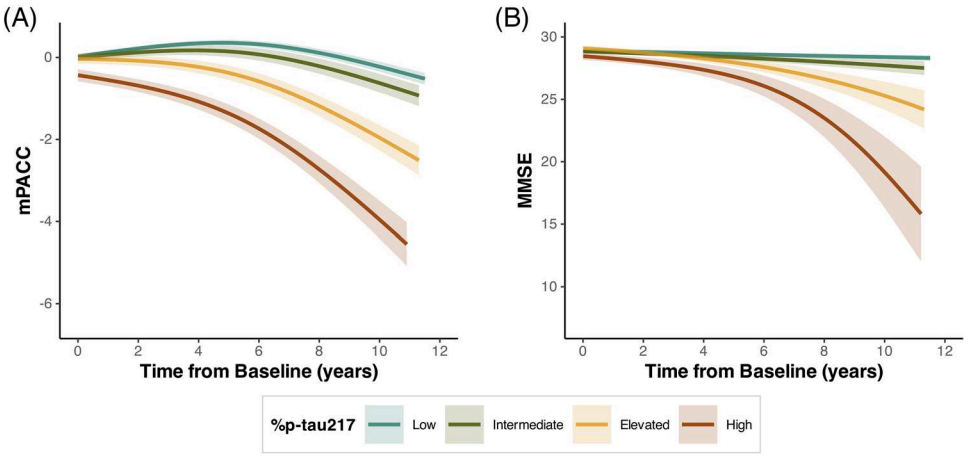

FIGURE 1 Modeled trajectories of cognitive outcomes, stratified by %p-tau217 levels (Low, Intermediate, Elevated, and High). (A) Modified Preclinical Alzheimer Cognitive Composite (mPACC). (B) Mini-Mental State Examination (MMSE). Models are controlled for age, sex, APOE ε4 carrier status, and years of education. Predictions are conditional on average/mode values of the covariates and plotted up to the maximum follow-up time per group. Shaded regions are 95% confidence intervals.

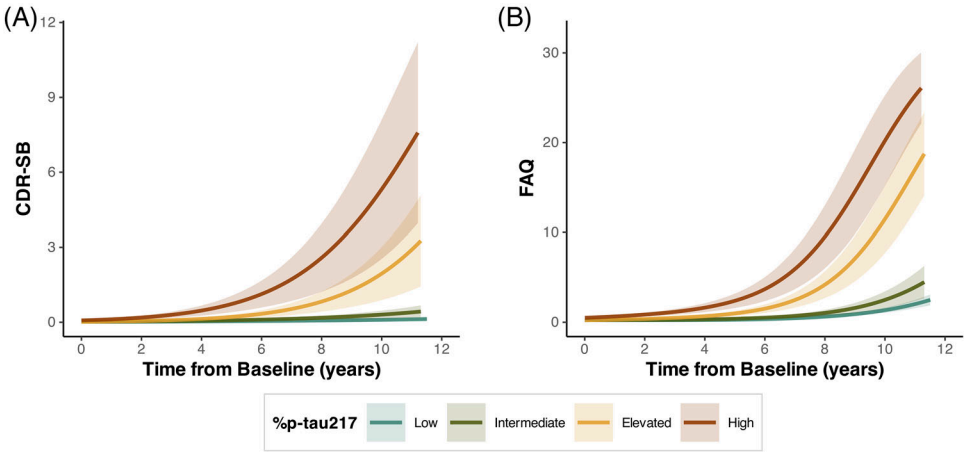

FIGURE 2 Modeled trajectories of clinical outcomes, stratified by %p-tau217 levels (Low, Intermediate, Elevated, and High). (A) Clinical Dementia Rating Sum of Boxes (CDR-SB). (B) Functional Activities Questionary (FAQ). Models are controlled for age, sex, APOE ε4 carrier status, and years of education. Predictions are conditional on average/mode values of the covariates and plotted up to the maximum follow-up time per group. Shaded regions are 95% confidence intervals.

the Low or Intermediate groups at baseline ($\Delta_{mPACC} < 0.05$ points, effect size < 0.08, $p > 0.470$) but exhibited notable mPACC decline after 5 years ($\Delta_{mPACC} > 0.52$ points, effect size > 0.58, $p < 0.001$) and substantial MMSE decline after 10 years ($\Delta_{MMSE} > 2.45$ points, effect size > 0.40, $p < 0.001$). By contrast, participants in the High group exhibited significantly lower baseline cognition compared to the other groups ($\Delta_{mPACC} \sim 0.4$ points, effect size ~ 0.6, $p < 0.001$) and presented the steepest longitudinal decline over time in both mPACC (5 years: $\Delta_{mPACC} > 0.99$ points, effect size > 1.10, $p < 0.001$) and MMSE (10 years: $\Delta_{MMSE} > 6.16$, points, effect size > 0.53, $p < 0.001$). Tables S1–S4 show mPACC and MMSE estimations and comparisons across all groups at baseline, 5 years, and 10 years. In a model-comparison analysis based on explained deviance, %p-tau217 alone accounted for 7.11% of the variance in mPACC trajectories and for a more modest 2.93% of the variance in MMSE trajectories, beyond demographic and genetic covariates.

3.2 | Clinical progression of %p-tau217 groups

Cognitive decline in the Elevated and High groups was paralleled by significant clinical (CDR-SB) and functional (FAQ) deterioration (Figure 2). Divergence against the Intermediate and Low groups became apparent as early as year 5 for the High group ($d > 0.38$, $p < 0.001$), though the degree of impairment was still modest ($\Delta_{CDR\text{-}SB} < 0.58$, $\Delta_{FAQ} < 2.14$). By year 10, both Elevated and High groups exhibited marked increases in FAQ and CDR-SB ($\Delta_{CDR\text{-}SB} > 1.56$, effect size > 0.68, $p < 0.001$; $\Delta_{FAQ} > 8.32$, effect size > 0.70, $p < 0.001$). Tables S5–S8 present CDR-SB and FAQ projections and comparisons across all groups at baseline, 5 years, and 10 years. %p-tau217 alone accounted for 9.72% of the variance in CDR-SB trajectories and for 6.70% of the variance in FAQ trajectories, beyond demographic and genetic covariates.

Overall rates of progression to MCI/dementia were 16.2% and 6.7%, respectively. Supplementary Figure S2 illustrates the distribution of %p-tau217 strata by future progression status (converters vs non-converters: $d = 0.71$, $p < 0.001$). In survival analyses (Figure 3), the Intermediate group showed moderately increased risks of MCI/dementia (HR = 2.4, CI = [1.4, 4.0]) and dementia (HR = 2.6, CI = [1.1, 6.1]) compared to the Low group. The Elevated and High groups showed markedly increased risks of MCI/dementia (Elevated vs Low: HR = 6.0, CI = [3.8, 9.7], High vs Low: HR = 12.6, CI = [7.9, 20.2]) and dementia (Elevated vs Low: HR = 9.9, CI = [5.0, 19.9], High vs Low: HR = 21.3, CI = [10.3, 43.8]). Tables S9–S10 show HR estimations across all group pairs.

The Low group showed high NPV for any clinical progression at 5 years (93.5%, CI = [91.4, 95.5]) and 10 years (92.2%, CI = [89.8, 94.5]) and for dementia at 5 (98.6%, CI = [98.0, 99.1]) and 10 years (98.1%, CI = [97.3, 99.0]). Conversely, the High group showed moderately high PPVs for progressing to MCI/dementia (5 years: 55.3%, CI = [39.8, 70.8]; 10 years: 71.6%, CI = [52.3, 90.1]) and even for progression to dementia (5 years: 32.0%, CI = [16.0, 48.1]; 10 years: 44.9%, CI = [23.6, 66.3]). Sensitivity was modest (<60% for Elevated/High), consistent with the low proportion of converters, but specificity remained consistently high (>89% for Low/Intermediate), aligning with the strong NPVs. Additional details, including sensitivity and specificity estimates for all the cut-offs, are provided in Tables S11–S16.

3.3 | Longitudinal neurodegeneration trajectories of %p-tau217 groups

Baseline %p-tau217 significantly predicted trajectories of HippVol, NfL, and GFAP ($p < 0.002$; Figure 4). Baseline HippVol was significantly lower for both High and Elevated groups compared to the Low group ($\Delta_{HippVol} > 0.05$, effect size > 0.26, $p < 0.017$), and both showed significantly accelerated atrophy over time (10 years vs Low: $\Delta_{HippVol} > 0.08$, effect size > 0.44, $p < 0.001$). The Low and Intermediate groups followed parallel trajectories of HippVol that did not diverge over time

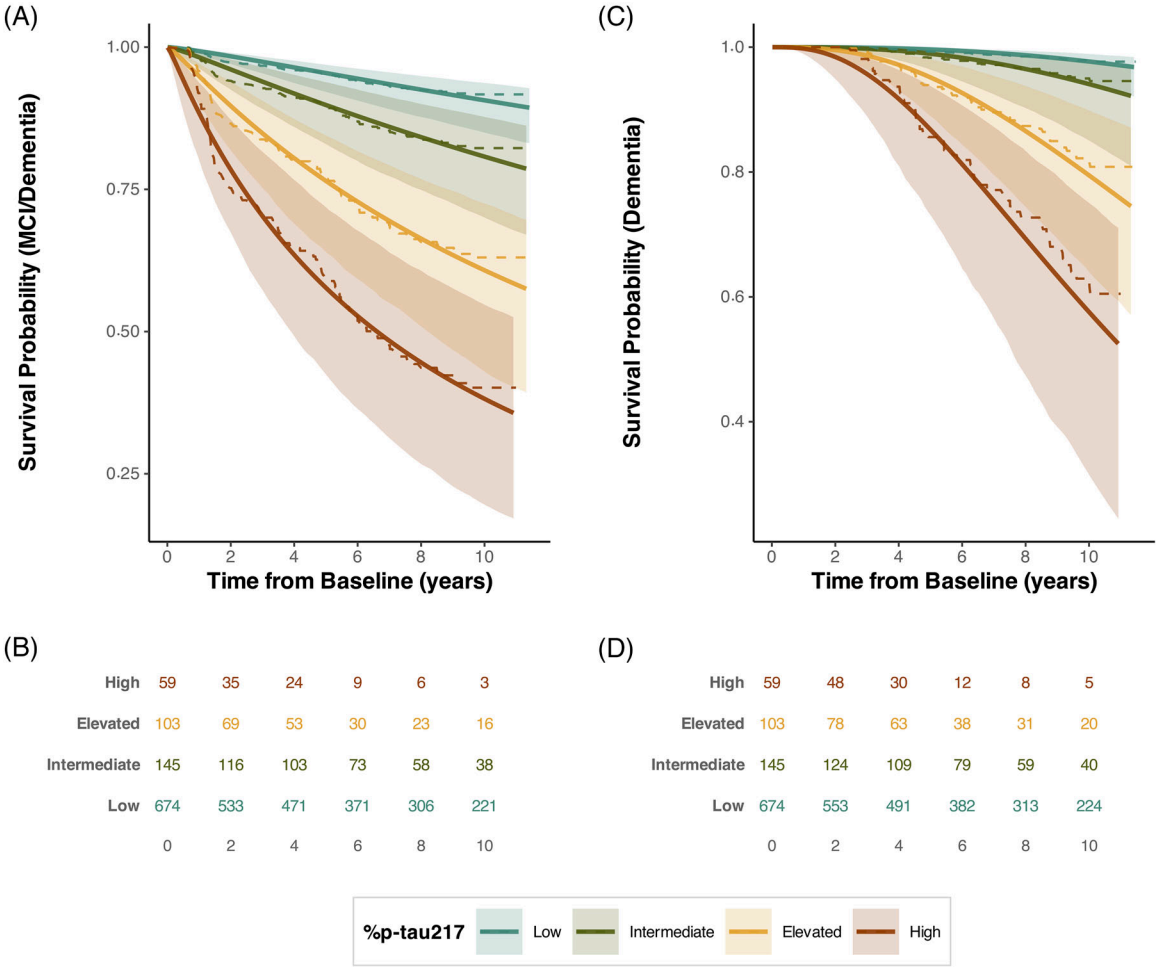

FIGURE 3 Modeled trajectories of clinical progression outcomes, stratified by %p-tau217 levels (Low, Intermediate, Elevated, and High). (A) Cox and parametric regression survival curves for progression to mild cognitive impairment (MCI) or dementia. (B) Number of individuals at risk over time for each %p-tau217 group at each time point in panel (A). (C) Parametric and Cox regression survival curves for progression to dementia. (D) Number of individuals at risk over time for each %p-tau217 group at each time point in panel (C). Models are controlled for age, sex, APOE ε4 carrier status, and years of education. Predictions are conditional on average/mode values of the covariates and plotted to the maximum follow-up time per group. Shaded regions are 95% confidence intervals.

($p > 0.125$). Baseline plasma NfL levels differed significantly only for High versus Low (effect size = 0.40, $p = 0.019$), while longitudinally, the High group displayed greater elevation compared to the remaining groups (10 years: $\Delta_{NfL} > 6.8$ pg/mL, effect size > 0.58, $p < 0.053$). Finally, plasma GFAP levels demonstrated clear baseline differences in neuroinflammation, with higher %p-tau217 groups being associated with progressively higher GFAP concentrations and all groups differing from the Low group (effect size > 0.50, $p < 0.001$). Longitudinally, the High group showed the steepest increase, diverging from the other groups over time (year 10: $\Delta_{GFAP} > 89$ pg/mL, effect size > 0.60, $p < 0.025$). Tables S17–S22 present HippVol, NfL, and GFAP estimations and comparisons across all groups at baseline, 5 years, and 10 years. Among neurodegeneration and astrocytic markers, %p-tau217 explained a modest fraction of the variance in hippocampal volume (1.15%) and NfL (1.95%) trajectories but accounted for a substantially larger share of the variance in GFAP trajectories (9.61%), beyond demographic and genetic covariates.

3.4 | Replication analyses

A total of 1011 CU participants from the VP cohort had sufficient plasma available for p-tau217$_{Fujirebio}$ measurements, including the 982 participants for whom %p-tau217 was quantified using LC-MS/MS. Despite comparable group sizes and baseline characteristics (Table S23), concordance between %p-tau217 and p-tau217$_{Fujirebio}$ was high only for the Low group (84.7%; Figure S3), whereas the Intermediate, Elevated, and High categories showed substantial reclassification. Notably, exhaustive cut-off-matching optimization failed to improve alignment, suggesting that these discrepancies likely reflect inherent assay differences rather than miscalibrated cut-offs (Supplementary Results 4).

Overall, cognitive trajectories based on p-tau217$_{Fujirebio}$ (Supplementary Results 4.1) closely mirrored those of %p-tau217. While the Intermediate group showed very modest progression compared to Low, both the Elevated and High p-tau217$_{Fujirebio}$ groups displayed

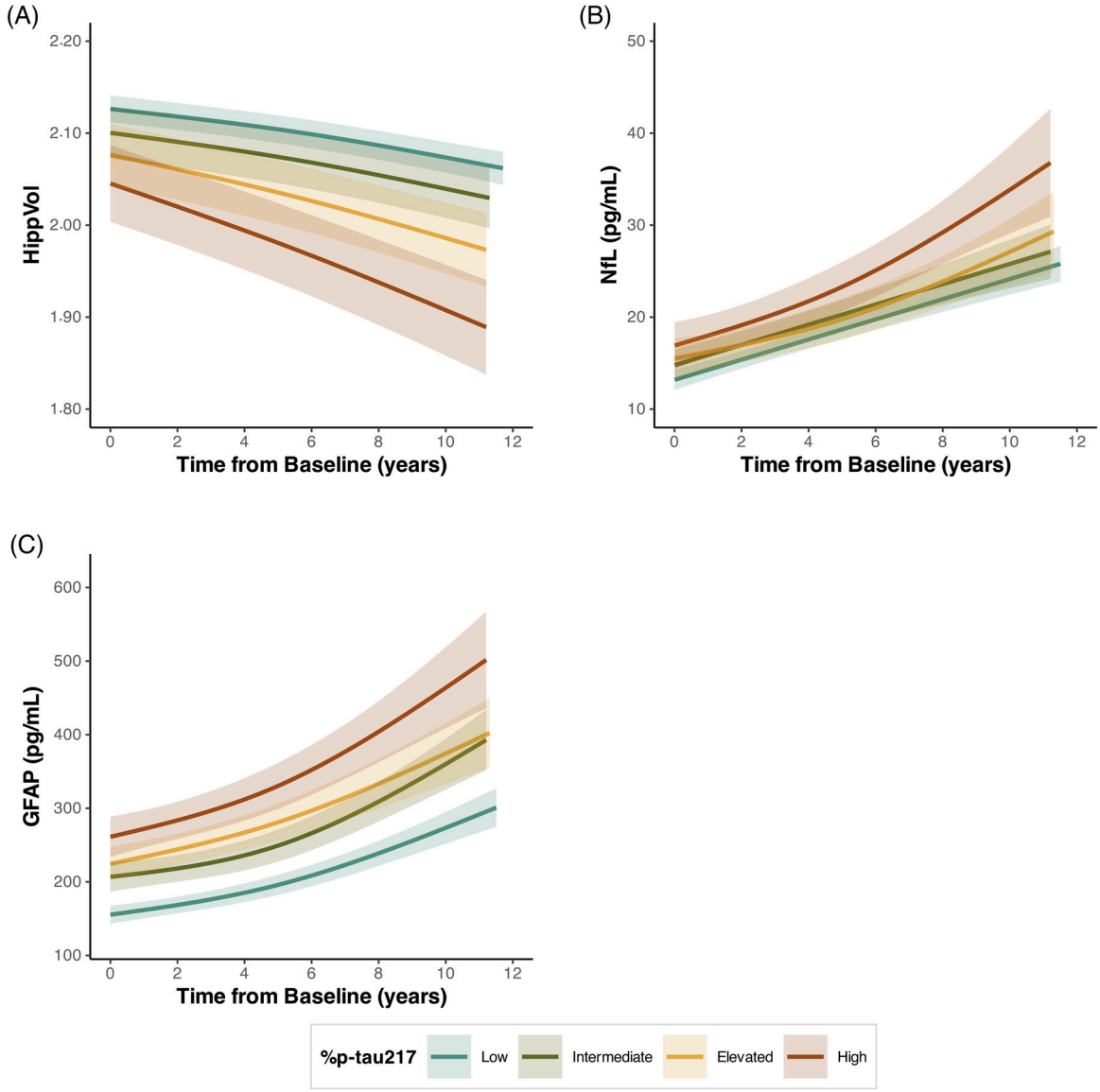

FIGURE 4 Modeled trajectories of neurodegeneration/neuroinflammation biomarker outcomes, stratified by %p-tau217 levels (Low, Intermediate, Elevated, and High). (A) Normalized hippocampal volume (HippVol). (B) Neurofilament light chain (NfL). (C) Glial fibrillary acidic protein (GFAP). All models are controlled for age, sex, APOE ε4 carrier status, and years of education. Predictions are conditional on average/mode values of the covariates and plotted up to the maximum follow-up time per group. Shaded regions are 95% confidence intervals.

significantly steeper cognitive decline compared to both Low and Intermediate. However, unlike for %p-tau217, differences between the Elevated and High p-tau217$_{Fujirebio}$ groups were narrower and non-significant ($p > 0.107$; Figure S4, Tables S24–27). As observed for %p-tau217, accelerated cognitive decline in these groups was accompanied by faster clinical and functional deterioration (Figure S5, Tables S28–S31).

Figure S6 shows the distribution of p-tau217$_{Fujirebio}$ strata by future progression status. Although group differences between converters and non-converters were more modest than for %p-tau217 ($d = 0.36$, $p < 0.001$ vs $d = 0.71$, $p < 0.001$), participants classified as Elevated or High exhibited similarly increased risks of progressing to MCI or dementia (HR > 7.5 vs Low; Supplementary Results 4.2, Figure S7, Tables S32–S33). NPVs for the Low group were also similar to those of %p-tau217: 92.6% (CI = [90.3, 94.8]) and 97.0% (CI = [95.3, 98.7]) for MCI and dementia at year 10, respectively, but PPVs for the High group were lower (for MCI/dementia: 54.2%, CI = [36.1, 72.3] vs 71.6%, CI = [52.3, 90.1] for %p-tau217). Additional details, including sensitivity and specificity estimates for all the cut-offs, are provided in Tables S34–S39. With p-tau217$_{Fujirebio}$, baseline differences across GFAP, NfL, and HippVol were largely replicated, and longitudinal HippVol was significantly different in both the Elevated and High groups compared to the Low group at 5 and 10 years (Table S41). However, longitudinal trajectories of plasma GFAP and NfL were less consistent

than those obtained with %p-tau217, particularly for the High group, which did not display the expected trajectory of accelerated increase (Supplementary Results 4.3, Figure S8, Tables S40–S45).

The model-comparison analysis based on explained deviance for p-tau217$_{Fujirebio}$ yielded estimates comparable to those of %p-tau217 (mPACC 6.74%, MMSE 2.90%, CDR-SB 8.76%, FAQ 5.95%, HippVol 2.38%, NfL 2.56%, GFAP 6.38%), supporting the broad consistency of both assays in explaining variance across outcomes.

Supplementary Results 5 detail the replication of our results on 1204 CU individuals from the AgeCoDe cohort (Table S46). Cognitive and clinical trajectories based on p-tau217$_{ALZPath}$ mirrored those of %p-tau217 and p-tau217$_{Fujirebio}$ (Supplementary Results 5.1, Figures S9–S10, Tables S47–S54). Notably, as for p-tau217$_{Fujirebio}$, the Elevated and High groups did not differ on mPACC* ($p > 0.150$). Survival analysis (Supplementary Results 5.2) showed lower HRs for High versus Low compared to %p-tau217 and p-tau217$_{Fujirebio}$ (for MCI/dementia: HR = 5.4, CI = [3.8, 7.6]; Figure S11, Tables S55 and S56), likely reflecting the higher MCI progression rates observed in the Low group. This pattern may be partially attributable to the substantially older baseline age in this cohort (83.7 vs 74.7 years in the VP). Consequently, the NPV for long-term (7.5 years) progression to MCI was lower in the AgeCoDe (79.8%, CI = [76.6, 83.0]), although the NPV for dementia remained high (91.7%, (CI = [89.5, 93.9]). The High group showed a PPV of 64.5% (CI [52.5, 76.5]) for MCI/dementia progression and 57.0% (CI [44.6, 69.3]) for dementia alone, accounting for death as a competing risk. Additional details are provided in Tables S57–S68.

Tables S69–S72 summarize NPV, PPV, sensitivity, and specificity results across all assays and cohorts, including a comparison between %p-tau217 and p-tau217$_{Fujirebio}$ restricted to the 982 individuals who share both measurements.

4 | DISCUSSION

In our community-based study, elevated plasma %p-tau217 in CU older adults was associated with faster cognitive decline, accelerated neurodegeneration, and an increased risk for clinically relevant progression.

Our results build on recent evidence linking higher levels of plasma p-tau217 with baseline differences in both cognition and neurodegeneration[10,14] and progressively steeper declines among CU individuals.[16–18] Baseline differences in cognition were modest, as expected by design, but higher %p-tau217 levels associated with other biomarkers (especially GFAP),[27] suggesting that %p-tau217 may be associated with early pathophysiological changes in preclinical AD. Longitudinally, higher %p-tau217 levels were associated with progressively faster cognitive decline, in good agreement with recent reports from clinical trials and community-based cohorts.[16,28] Interestingly, although the Intermediate group showed baseline signs of early cognitive and neurodegenerative changes, their progression, while still clearly distinct from that of the Low group, remained relatively modest. By contrast, the Elevated and High groups exhibited faster hippocampal atrophy, paralleled by accelerated cognitive decline and functional and clinical deterioration. It is important to note that plasma p-tau217 increases are linked, almost equally, to Aβ and tau accumulation,[29] so subjects with the highest values, as observed in the Elevated and High groups, are expected to have the highest risk of presenting with tau pathology,[25] whereas increased %p-tau217 in the Intermediate group may primarily reflect amyloid pathology.[24] Thus, our results are in good agreement with recent evidence suggesting that tau pathology is more tightly linked to clinical progression and neurodegeneration in CU individuals.[10,30,31] In this context, our results strongly suggest that only CU individuals with substantially elevated %p-tau217 levels may be considered to be at risk of clinically meaningful decline, even in the long term. These findings also support the potential utility of %p-tau217 for plasma biomarker-based disease staging and risk stratification.[18]

In our community setting, low levels of %p-tau217 had notable NPV for any clinical progression, even at 10 years (92.2%), supported by relatively high specificity. These findings highlight the potential of plasma %p-tau217 as a front-line screening tool capable of reassuring most CU individuals of their low risk of future decline, while enabling a more efficient allocation of resources for confirmatory follow-up. Moreover, p-tau217$_{Fujirebio}$ and p-tau217$_{ALZPath}$ showed comparable NPVs, reinforcing the feasibility of implementing these screening strategies using more accessible immunoassays. On the other hand, high %p-tau217 levels led to PPVs > 70% for progression to MCI or dementia, which lies between previously reported PPVs for amyloid and tau PET.[31–33] These PPVs, together with good specificity estimates, indicate that elevated %p-tau217 concentrations can identify a subset of CU individuals with a substantially increased likelihood of clinical progression. However, the low sensitivity at these high cut-offs implies that only a minority of future converters would reach such extreme %p-tau217 values, underscoring the need for more comprehensive predictive models to accurately identify individuals at risk of progression.[34] Conversely, we also observed a subset of future converters who showed low plasma %p-tau217 levels (Figure S2), suggesting that cognitive decline in some CU individuals may be driven by processes not captured by AD-specific biomarkers and that the inclusion of complementary, non-AD biomarkers may improve the performance of future prognostic models. Consistent with this view, our variance-decomposition analysis showed that, while both plasma %p-tau217 and p-tau217$_{Fujirebio}$ explained a meaningful fraction of the longitudinal variability in cognitive, clinical, and astrocytic biomarker trajectories (~6-10%), a substantial portion of the variance remained attributable to other factors. These findings, which are broadly consistent with those in previous studies,[10] highlight the complexity of predicting clinical progression in CU older adults and underscore the need for multimodal prognostic strategies integrating both AD-specific and non-AD indicators.

Relevantly, p-tau217$_{Fujirebio}$ showed substantially lower PPVs than %p-tau217 in the same cohort, consistent with prior findings.[18] Moreover, although p-tau217$_{ALZPath}$ showed higher PPVs compared to p-tau217$_{Fujirebio}$, these were conditioned by higher overall progression rates in the AgeCoDe cohort. Notably, %p-tau217 revealed clear differences between the Elevated and High categories across most

outcomes, unlike immunoassays, and correlated more tightly with the expected neurodegenerative course of the disease, especially for the High group. Consistently, %p-tau217 explained a larger fraction of the variance in GFAP trajectories (9.61%) than p-tau217$_{Fujirebio}$ (6.38%), further supporting its tighter pathophysiological coupling. Together, these results suggest that the tested immunoassays may have limited stratification capabilities at their upper dynamic ranges compared with %p-tau217. This is in agreement with recent comparisons showing that %p-tau217 outperforms immunoassay results in tracking amyloid and tau burden during disease progression.[14,15] These findings may have important implications not only for the use of %p-tau217 as a prognostic marker, but also for the enrichment of clinical trials in preclinical populations. In particular, our results suggest that trials enrolling CU individuals based on plasma %p-tau217 may benefit from higher cut-offs beyond conventional dual cut-point approaches, aimed at identifying participants more likely to show accelerated cognitive and neurodegenerative trajectories. Notably, our findings also reveal that these stratification capabilities may be assay-dependent, so enrichment strategies based on plasma biomarkers should be driven by careful decision-making.

Our study also has some limitations. First, dropout rates were relatively high compared to other community-based studies.[18] While dropout reasons are undetermined, high rates could reflect rapid decline or death, potentially biasing progression estimates. Moreover, annual follow-ups were interrupted for up to 2 years due to the COVID-19 pandemic. In addition to reducing the granularity of longitudinal trajectories, the effect of the pandemic on aging populations is a subject of ongoing research. Social isolation, reduced physical and cognitive activity, and even COVID-19 infection itself may accelerate cognitive decline in older adults.[35,36] Future studies may investigate the interaction between p-tau217 biomarkers and COVID-19. Additionally, we acknowledge that the interpretability of our results is constrained by the lack of confirmation of amyloid and tau status via PET or CSF. However, we note that the proportions of participants exceeding the pre-specified cut-offs for amyloid (31%) and tau (17%) are well aligned with expected prevalences for our age range.[31,37] Moreover, several previous studies have validated p-tau217 measurements against PET and CSF.[10,18] Finally, as for most of the previous studies in the field, we report data from demographically narrow cohorts. Future work should replicate these findings across more diverse groups, as emphasized by recent trials and position papers.[16,38]

Altogether, our results provide compelling evidence that plasma %p-tau217 is a robust biomarker for identifying CU individuals at both low and high risk of AD-related decline, associating with clinically relevant long-term differences in cognitive performance, clinical deterioration, and neurodegeneration. Immunoassays offer comparable NPVs and could facilitate broader screening for identifying low-risk individuals. Overall, these results support incorporating plasma p-tau217 testing into risk-stratification strategies for preclinical AD in both clinical practice and research.

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CONFLICT OF INTEREST STATEMENT

Jesús Silva-Rodríguez is a consultant, stakeholder, and board member of Qubiotech Health Intelligence. A.M. is an employee of ZRO Imaging AB. Andreas Jeromin is a former employee of ALZ path, Inc., holds stock options, and is a co-founder of Tau Biosciences, Inc., in which he holds stock options. All other authors declare no competing interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Written informed consent was obtained for all participants prior to being included in the study. The study was approved by the corresponding ethics committees of the respective institutions. The study was conducted in accordance with the Declaration of Helsinki and applicable local regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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