A Comparison of Levels and Longitudinal Trends of p-Tau 217 with MMSE, ADAS-Cog, and CDR in a Cohort of 113 Cognitively Normal and Cognitively Impaired Individuals Over 6 Years Using ADNI Data Set

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INTRODUCTION

FDA's approval of the plasma P-Tau217/ß-amyloid 1-42 ratio test has increased interest in blood-based biomarkers for Alzheimer's disease (AD), offering a less invasive alternative to PET imaging or lumbar punctures. While some literature shows high diagnostic accuracy for plasma P-Tau217 in detecting amyloid pathology1, others caution against full adoption, citing limitations in reliability and clinical applicability.

Moreover, despite the historical role of cognitive assessments, like MMSE, ADAS Cog, and CDR, in tracking AD, few studies explore longitudinal relationships with plasma P-Tau217. This lack of data raises questions about whether P-Tau217 reflects functional cognitive decline or merely tracks underlying pathology without capturing symptom progression. As the use of plasma biomarkers expands in clinical and research settings, it is essential to investigate the correlation between P-Tau217 and cognitive decline. We hypothesized that in cognitively impaired individuals, longitudinal changes in plasma P-Tau217 levels would significantly correlate with cognitive and functional decline, as measured by cognitive assessment scores.

METHODS

We utilized open-source data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) from 2005-2013, including 121 participants with P-Tau217 data. For this analysis, we included participants with reported plasma P-Tau217 values and corresponding cognitive assessments (MMSE, ADAS 11, ADAS 13, and CDR). Participants were stratified into Cognitively Normal (CN) and Cognitively Impaired (CI). CI includes, as defined by ADNI and board-certified psychiatrist evaluations, Subjective Memory Complaints, Early and Late Mild Cognitive Impairment, Mixed MCI, and AD3

We calculated the means and standard deviations for P-Tau217 and cognitive scores at each time point, excluding months where only one patient had data. Data tabulation began at month 48, when P-Tau 217 was first collected in ADNI. Net changes in both biomarker and cognitive scores were calculated from the first to the final visit (month 120) for each group.

Linear regression analyses were performed for both the CN and CI cohorts to examine longitudinal trends and assess the relationship between changes in PTau217 levels and MMSE.

RESULTS

Out of 121 participants, 113 were included in our analysis, with 40.71% females and 59.29% males. The mean age and median age were 71.9. At month 48 for each patient, P-Tau 217 data were available for 24 cognitively normal (CN) and 39 cognitively impaired (CI) participants. Throughout the study, an additional 12 CN and 38 CI participants joined the dataset. At month 120, 4 CN and 5 CI participants had available data for both P-Tau217 and cognitive assessments.

RESULTS

Table 1: Demographic Characteristics at Baseline for Cognitively Normal and Cognitively Impaired Subjects Included in the Study at Baseline

	Cognitively Normal (CN)	Cognitively Impaired (CI)
N	43	86
Female	40.7%	40.7%
Mean age	71.9	71.9
P-Tau217 (pg/mL)	0.07 ± 0.05	0.08 ± 0.06
MMSE	29.0 ± 1.4	26.7 ± 3.8
ADAS-Cog11	4.2 ± 2.2	10.54 ± 8.5
ADAS-Cog13	6.6 ± 3.9	15.9 ± 12.1
CDR	0.08 ± 0.3	0.4 ± 0.4

Over a 72-month follow-up period, we examined how participants' p-tau217 levels evolved in relation to changes in MMSE, ADAS-Cog11, ADAS-Cog13, and CDR scores.

Table 2: Longitudinal Changes in P-Tau 217 and Cognitive Measures from Month 48 to Month 120 Along With Percentage Changes Stratified by Cognition

Measure	Group	Baseline Mean	Final Mean	Absolute Δ	% Change
P-Tau217 (pg/mL)	CN	0.066	0.070	+0.003	**+4.5 %**
	CI	0.078	0.126	+0.048	**+61.5 %**
MMSE	CN	29.0	28.5	−0.5	**−1.7 %**
	CI	26.74	20.0	−6.74	**−25.2 %**
ADAS-Cog11	CN	4.22	9.60	+5.38	**+127 %**
	CI	10.54	25.33	+14.79	**+140 %**
ADAS-Cog13	CN	6.56	16.75	+10.19	**+155 %**
	CI	15.85	36.73	+20.88	**+132 %**
CDR	CN	0.08	0.25	+0.17	**+212 %**
	CI	0.41	0.80	+0.39	**+95 %**

Linear regression analyses for CN showed an increase in P-Tau217 (slope = $1.47e^{-4}$, $R^2 = 0.055$) and a decline in MMSE (slope = −0.0048, $R^2 = 0.012$); for CI, P-Tau217 also increased (slope = $2.47e^{-4}$, $R^2 = 0.008$) and MMSE declined (slope = −0.069, $R^2 = 0.108$).

Figure 1. Longitudinal Trends of P-Tau217 for 43 Cognitively Normal and 86 Cognitively Impaired Participants Over a 72-Month Period, From Month 48 to Month 132 Post-Baseline

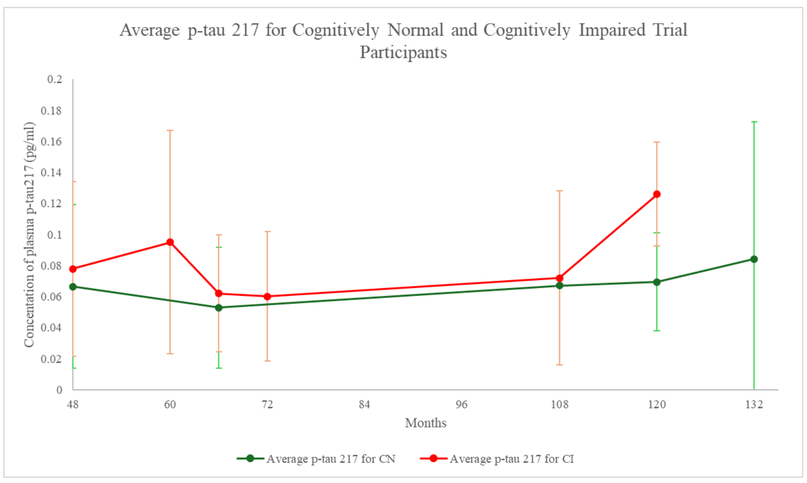
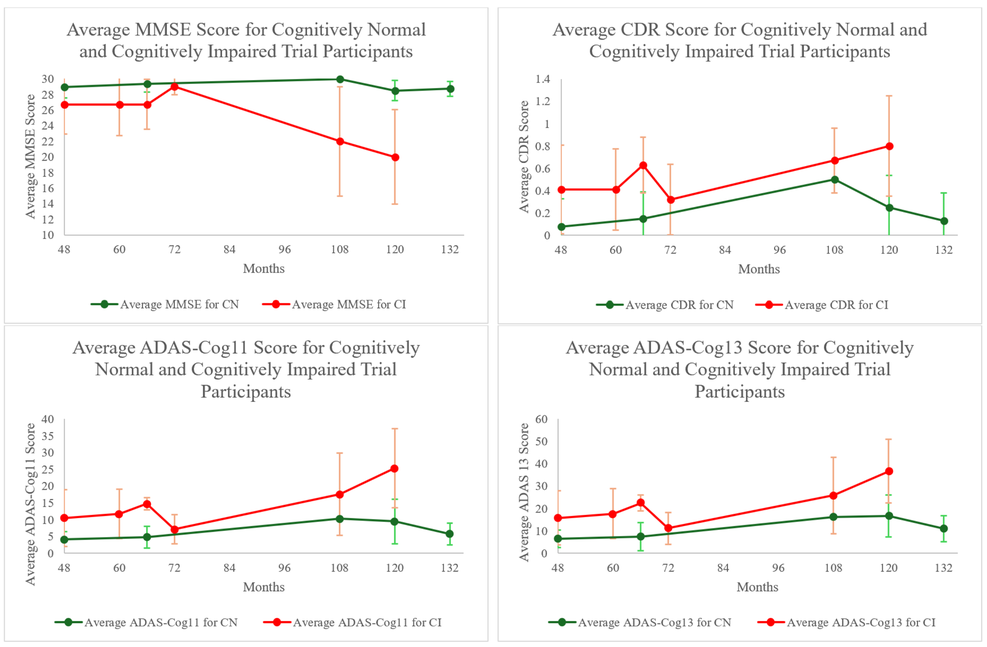


Figure 2. Longitudinal Trends of MMSE, ADAS-Cog11, ADAS-Cog13, and CDR Scores for 43 Cognitively Normal and 86 Cognitively Impaired Participants Over a 72-Month Period, From Month 48 to Month 132 Post-Baseline



SUMMARY

Open source ADNI data was analyzed for this current study and all subjects with at least 2 P-TAU 217 values and corresponding cognitive scores were included in our analysis. While plasma P-Tau217 is strongly associated with Alzheimer's pathology, our 6-year longitudinal analysis suggests it does not reliably reflect cognitive or functional decline. Although P-Tau217 levels were generally higher in CI participants than CN ones, these differences were not statistically significant. Across 9 visits, P-Tau217 trajectories showed inconsistent correlation with MMSE and other cognitive scores, especially in the CN group.

Linear regression of P-Tau217 and MMSE slopes revealed an inverse relationship; biomarker levels rose as MMSE scores declined, but low R^2 values (≤ 0.108)

indicated weak, non-predictive associations. Even at later timepoints, any observed differences lacked strong predictive value.

CONCLUSION

These findings suggest that while P-Tau217 may indicate underlying pathology, it is limited as a standalone diagnostic or monitoring tool. Relying on it alone could risk excluding individuals with meaningful symptoms from care or trial eligibility.

The study had limitations: the sample size declined over time, and averages at each wave reflected different individuals rather than a consistent cohort. Additionally, the ADNI dataset, drawn from a research setting, may not generalize well to the broader population. More research is needed to clarify P-Tau217's role and assess its

longitudinal utility.

REFERENCES

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