



# A Probability of Amyloid Positivity Model Incorporating p-tau 217 and Aβ42 for Identification of Preclinical Alzheimer’s Disease

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## BACKGROUND

- Alzheimer’s Disease (AD) develops over a prolonged preclinical phase during which amyloid pathology accumulates ~15-20 yrs before the onset of cognitive symptoms.
- Identifying amyloid pathology in asymptomatic individuals may provide a critical window for interventions aimed at preventing or delaying cognitive decline.
- Two ongoing clinical trials evaluating amyloid-modifying immunotherapies in preclinical, asymptomatic AD raise the possibility that these therapies may eventually be approved for biomarker-positive, cognitively unimpaired (CU) individuals<sup>1,2</sup>. If these trials prove successful, scalable approaches for identifying amyloid pathology in CU individuals will be desirable.

## OBJECTIVES

- Evaluate the performance of plasma p-tau217 and the p-tau217/Aβ42 ratio for predicting an abnormal amyloid PET in CU individuals.
- Establish clinically relevant thresholds for identifying CU individuals with AD pathology.

## METHODS

### COHORTS

**Mayo Clinic Study of Aging (MCSA)**<sup>3</sup>  
1856 [480 amyloid positive (A+)] participants 60–90 years old, CU at their first study visit, and an amyloid-PET imaging and blood sample collection performed.

**Alzheimer’s Disease Neuroimaging Initiative (ADNI)**<sup>4</sup>  
565 [151 A+] participants 60–90 years old, CU at their first study visit, and had both amyloid-PET imaging and Fujirebio Lumipulse plasma p-tau217, Aβ42, and Aβ40 data available.

### ASSAYS

Fujirebio Lumipulse plasma p-tau217, Aβ42, and Aβ40 immunoassays.

### DATA ANALYSIS

Logistic regression models using log2-transformed data were generated as predictors of brain amyloid pathology determined by amyloid-PET (A+, ≥25 Centiloid). Models were validated using data from ADNI. Area under the receiver operating characteristic curve (AUC) was computed for each model. Probability of Amyloid Positivity Scores (PAPS) were computed for the p-tau217 and p-tau217+ Aβ42 models and cutpoints for positive, negative, and intermediate amyloid status were established, alongside binary cutpoints.

## RESULTS

Figure 1: Forest plot of AUCs for models predicting amyloid positivity in CU individuals

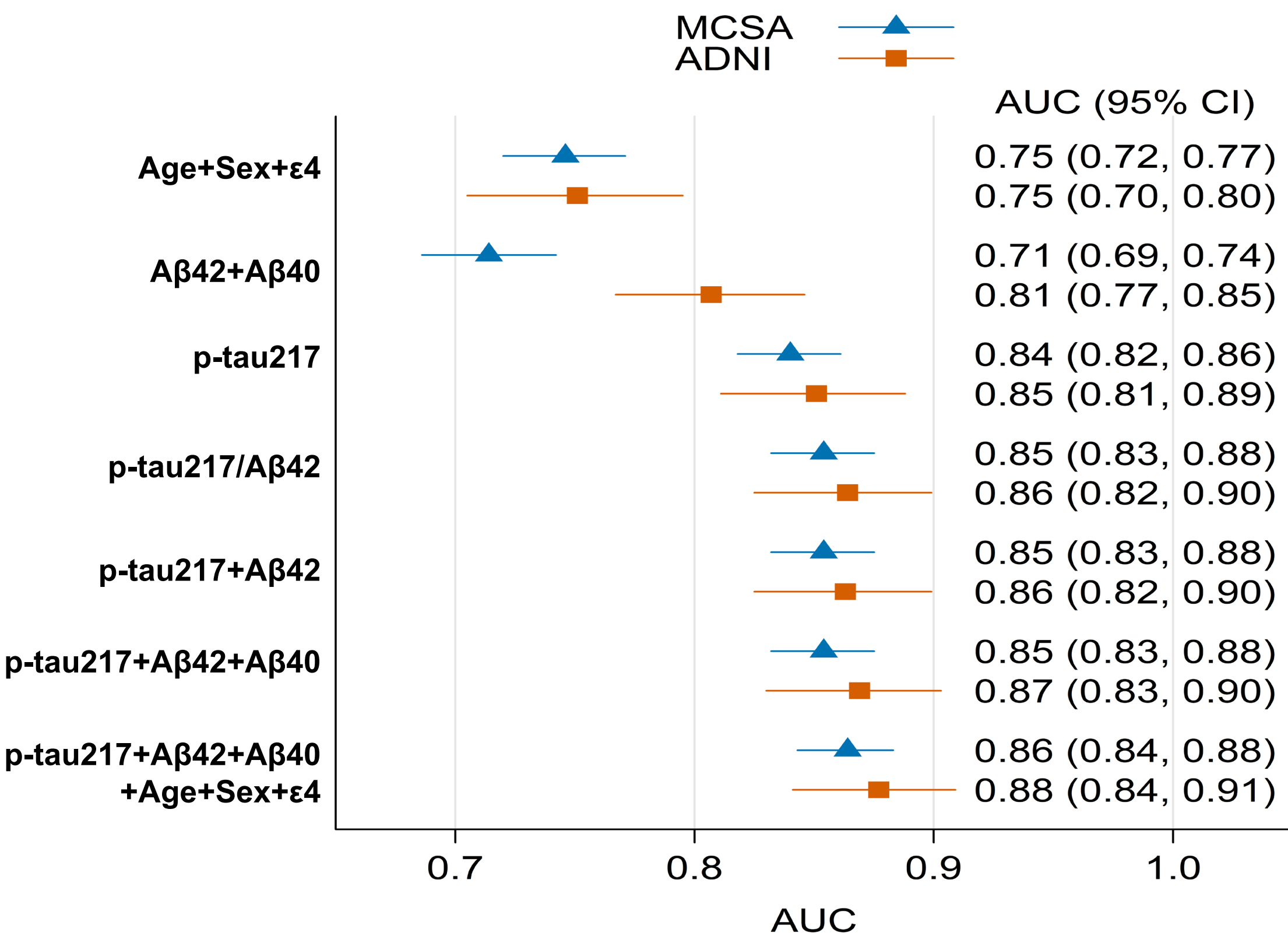


Table 1: One-cutpoint probability of amyloid positivity score incorporating plasma p-tau217 or p-tau217 plus Aβ42.

| Model                        | Cohort | Sensitivity  | Specificity  | PPV          | NPV          | Accuracy     |
|------------------------------|--------|--------------|--------------|--------------|--------------|--------------|
| log2(ptau217)                |        |              |              |              |              |              |
| One-cutpoint @95 specificity | MCSA   | 41% (37, 45) | 95%          | 77% (72, 82) | 80% (78, 82) | 79% (77, 81) |
|                              | ADNI   | 41% (34, 49) | 95% (93, 97) | 76% (65, 84) | 82% (78, 85) | 81% (77, 84) |
| One-cutpoint @95 sensitivity | MCSA   | 95%          | 31% (28, 34) | 36% (33, 39) | 94% (91, 96) | 50% (47, 52) |
|                              | ADNI   | 93% (87, 96) | 49% (44, 54) | 40% (35, 45) | 95% (91, 97) | 61% (57, 65) |
| log2(ptau217)+log2(Aβ42)     |        |              |              |              |              |              |
| One-cutpoint @95 specificity | MCSA   | 41% (37, 46) | 95%          | 78% (72, 82) | 80% (78, 82) | 80% (78, 81) |
|                              | ADNI   | 36% (29, 44) | 97% (94, 98) | 79% (68, 87) | 81% (77, 84) | 80% (77, 83) |
| One-cutpoint @95 sensitivity | MCSA   | 95%          | 34% (32, 37) | 37% (34, 40) | 94% (92, 96) | 52% (49, 54) |
|                              | ADNI   | 89% (84, 93) | 60% (56, 65) | 45% (40, 51) | 94% (91, 96) | 68% (64, 72) |

Prevalence of amyloid pathology was 29% for MCSA and 27% for ADNI. Values in parentheses are 95% confidence intervals. Confidence intervals are purposely omitted for the predefined parameters.

Table 2: Two-cutpoints probability of amyloid positivity score incorporating plasma p-tau217 or p-tau217 plus Aβ42.

| Model                                        | Cohort | PPV          | NPV          | Accuracy     | Intermediates |
|----------------------------------------------|--------|--------------|--------------|--------------|---------------|
| log2(ptau217)                                |        |              |              |              |               |
| Two-cutpoint @85 specificity and specificity | MCSA   | 73% (68, 77) | 93% (91, 95) | 86% (83, 88) | 39% (36, 41)  |
|                                              | ADNI   | 73% (64, 80) | 94% (91, 96) | 88% (85, 91) | 28% (25, 32)  |
| log2(ptau217)+log2(Aβ42)                     |        |              |              |              |               |
| Two-cutpoint @85 specificity and specificity | MCSA   | 73% (69, 77) | 93% (91, 95) | 86% (84, 88) | 26% (24, 28)  |
|                                              | ADNI   | 76% (67, 82) | 94% (91, 96) | 89% (86, 91) | 18% (15, 21)  |

Prevalence of amyloid pathology was 29% for MCSA and 27% for ADNI. Values in parentheses are 95% confidence intervals.

## CONCLUSIONS

- Plasma p-tau217 was the strongest predictor of amyloid pathology in CU individuals. And showed consistent performance across MCSA and ADNI.
- Adding Aβ42 provided little improvement in overall discrimination or diagnostic accuracy but reduced the proportion of intermediate results when a two-cutpoint approach was used.
- p-tau217–based probability models may serve as scalable tools for identifying AD pathology in CU individuals.

## REFERENCES

- Yaari R, Holdridge KC, Williamson M, et al. *Alzheimers Dement.* 2025;21(9):e70662.
- Rafii MS, Sperling RA, Donohue MC, et al. *Alzheimer's Dement.* 2023;19(4):1227-1233.
- Roberts RO, Geda YE, Knopman DS, et al.. *Neuroepidemiology.* 2008;30(1):58-69.
- Weiner MW, Kanoria S, Miller MJ, et al. *Alzheimers Dement.* 2025;21(1):e14321.