

Predicting onset of Alzheimer disease symptoms with the interaction of plasma %p-tau217 and age combined with brain volumes

Kellen K. Petersen, PhD¹
Suzanne E. Schindler, MD, PhD¹

¹ Department of Neurology
Washington University School of Medicine
St. Louis, MO, USA



OBJECTIVE

To determine whether adding MRI brain volumes to a plasma %p-tau217 and age interaction model improves prediction of the timing and risk of Alzheimer's disease symptom onset in cognitively unimpaired individuals.

HYPOTHESIS

Brain volumes measured by MRI may reflect co-pathologies or resilience factors not captured by plasma %p-tau217 alone, and could therefore improve prediction of AD symptom onset beyond %p-tau217 and age.

CONCLUSIONS

- Adding 9 MRI volumetric measures to the plasma %p-tau217*age interaction model improved survival discrimination from a C-index of 0.689 to 0.768, a gain of 0.079.
- Risk stratification with MRI yielded a 13.2-fold difference in 10-year progression probability between high- and low-risk groups versus 6.9-fold without MRI.
- Selected MRI regions including anterior cingulate, orbitofrontal cortex, and ventricular measures may reflect early neurodegeneration or co-pathologies not captured by plasma biomarkers, with potential utility for trial enrichment and preventive intervention targeting.

kellenpetersen@wustl.edu

INTRODUCTION

Using plasma %p-tau217 clock models, we previously found that older age at %p-tau217 positivity is associated with a shorter time until onset of Alzheimer's disease (AD) symptoms. We hypothesized

METHODS

- Cognitively unimpaired individuals (CDR=0) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with baseline plasma %p-tau217 and MRI data were analyzed.
- To predict development of symptomatic AD (CDR>0 with diagnosis of AD), we developed random survival forest models with forward variable selection using plasma %p-tau217, age, the

RESULTS

- 173 initially cognitively unimpaired ADNI participants had an average age of 74.5 ± 6.5 years. Over 8.4 ± 3.6 years of cognitive follow-up, 28 (16.2%) developed symptomatic AD. Progressors were older (77.6 vs 73.9 years) with higher baseline %p-tau217 (6.1% vs 3.2%).
- A model with plasma %p-tau217, age, and the %p-tau217*age interaction achieved a C-index of 0.689 (95% CI: 0.529-0.838). A 12-predictor model with %p-tau217, age, the %p-tau217*age interaction, and 9 selected MRI measures achieved a C-index of 0.768, improving discrimination by 0.079 (**Figure 1**).
- Selected MRI volumetric measures were the left precentral gyrus, right rostral and caudal anterior cingulate, right inferior lateral ventricle, third ventricle, right cerebellar cortex, left pars orbitalis, right medial orbitofrontal cortex, and right frontal pole (**Figure 2**).
- Risk stratification by predicted risk percentiles showed 10-year KM-estimated progression probabilities of 52.3% (high) vs 4.0% (low) with MRI, and 44.2% vs 6.4% without MRI (**Figure 3**). Among progressors, predicted age at onset had cross-validated R²=0.66 and MdAE=2.6 years (MAE=3.2, RMSE=3.8 years).

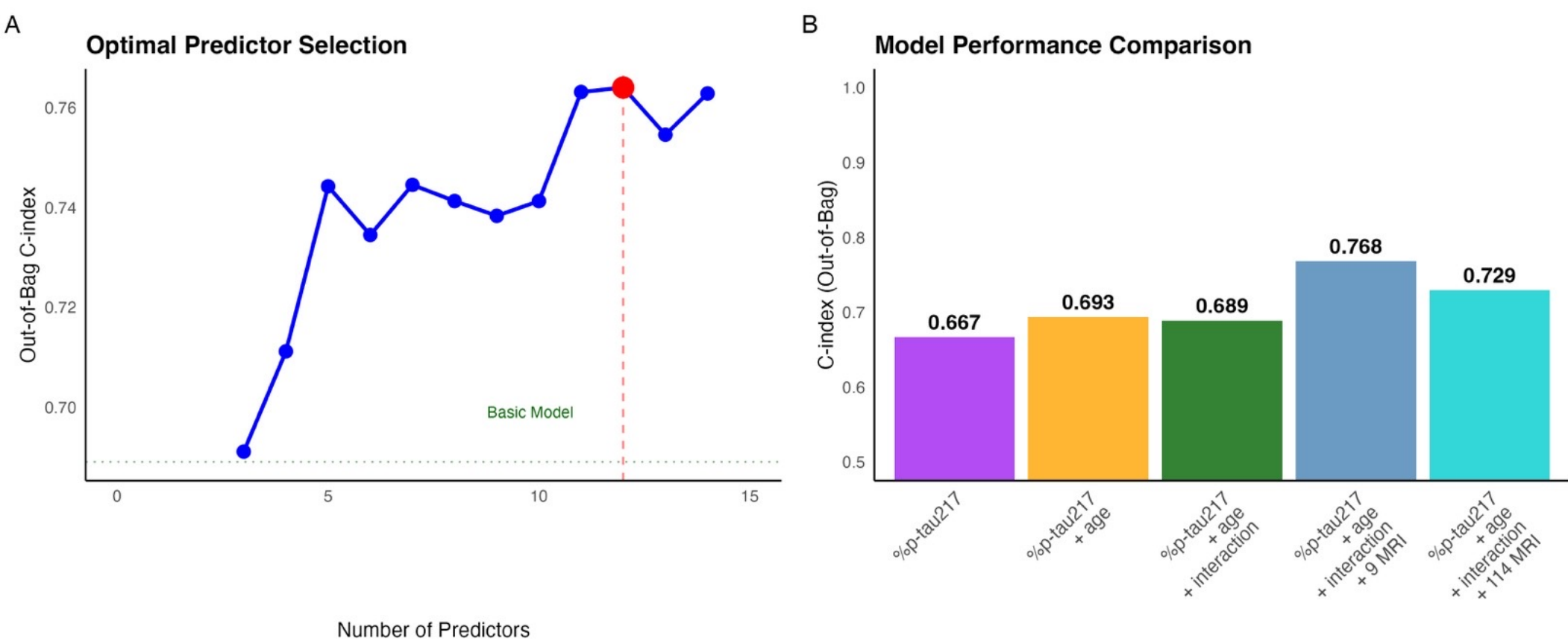


Figure 1. Predictor selection and model performance comparison. (A) Out-of-bag C-index across predictor counts, with the optimal model selected at 12 predictors (out-of-bag C-index=0.764). (B) Performance comparison across models, with the optimal 12-predictor model achieving the highest discrimination (bootstrap-validated C-index=0.768).

that brain volumes as measured by MRI might reflect co-pathologies that affect the relationship between %p-tau217 levels, age, and risk for developing AD symptoms.

- %p-tau217*age interaction, and 114 ICV-normalized brain volumes. Models were validated via 1000 bootstrap iterations.
- To predict timing of symptom onset, selected predictors were applied to linear regression models trained on progressors, with performance assessed using leave-one-out cross-validation.

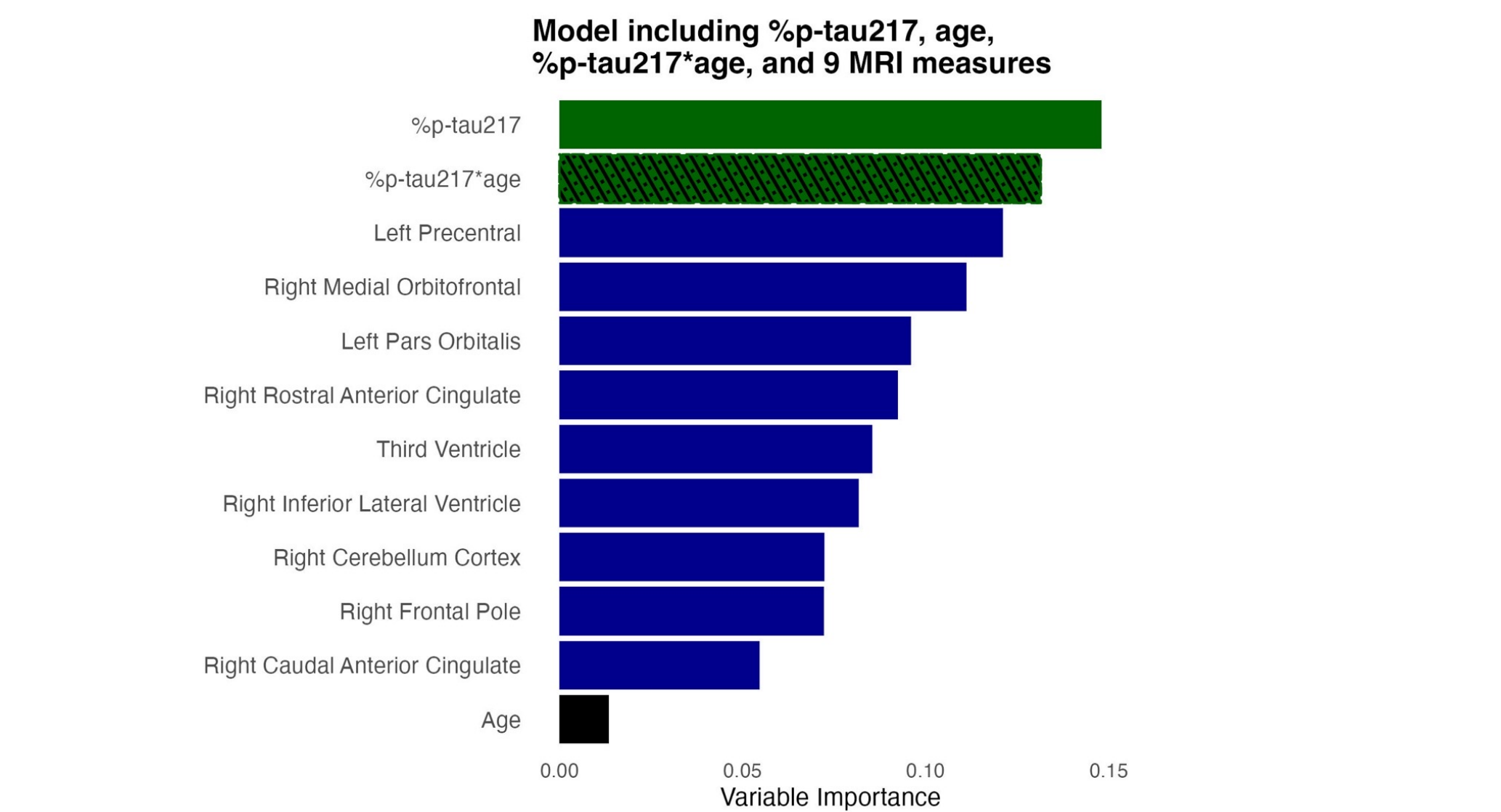


Figure 2. Variable importance of predictors of risk for development of AD symptoms. The model included plasma %p-tau217, age, the %p-tau217*age interaction, and selected MRI measures. Top predictors were %p-tau217, the %p-tau217*age interaction, and nine cortical/ventricular volumes.

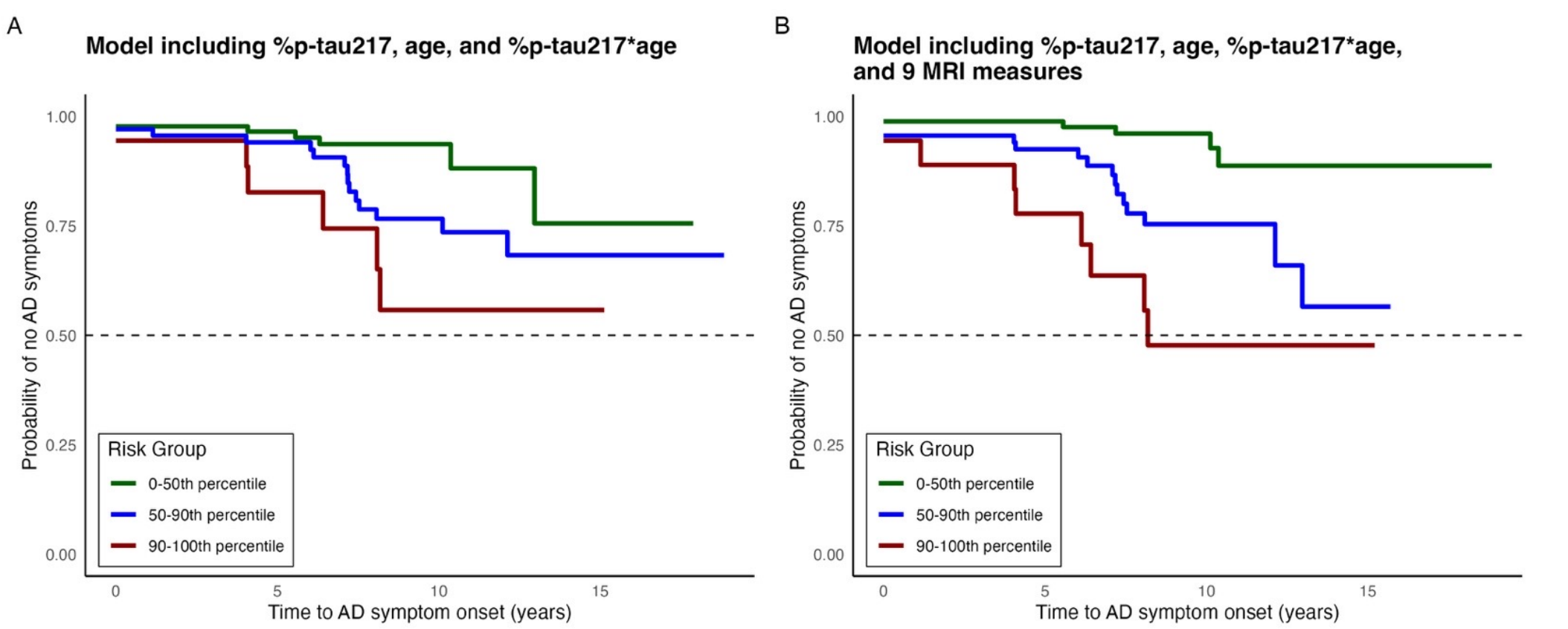


Figure 3. Risk stratification for progression to AD symptom onset. Kaplan-Meier curves for (A) A model with plasma %p-tau217, age, and %p-tau217*age interaction and (B) A model with 12 predictors of %p-tau217, age, %p-tau217*age, and 9 MRI volumetric measures stratified participants into three risk groups based on predicted risk for development of AD symptoms (0-50th, 50-90th, and 90-100th percentiles). The model with MRI measures achieved superior risk separation with 10-year KM-estimated progression probability of 52.3% in the high-risk group compared to 4.0% in the low-risk group (13.2-fold difference), while the model without MRI measures showed 44.2% versus 6.4% (6.9-fold difference).