

Prevalence and Longitudinal Dynamics of Alpha-synuclein Co-pathology in ADNI

A Cross-sectional And Longitudinal SAA Study

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High Sensitivity

97% Specificity and 79% Sensitivity for Lewy body (LB) pathology validated against autopsy.



Stage Dependent

Prevalence increases with disease severity: 16% in cognitively unimpaired to 38% in dementia.



Earlier Onset

SAA+ individuals reach cognitive impairment 4.7–9.3 years earlier than SAA– counterparts.

Background & Motivation

The coexistence of Alzheimer's disease (AD) and Lewy body (LB) pathology is a frequent finding at autopsy and significantly contributes to clinical heterogeneity.

While amyloid- β ($A\beta$) and tau are defining hallmarks, the *in vivo* dynamics of α -synuclein (α -syn) co-pathology remain less understood.

Goal: Evaluate prevalence and longitudinal dynamics of mixed $A\beta/\alpha$ -syn pathology using CSF α -syn seed amplification assays (SAA).

Methods & Cohort

Participants

1,638 ADNI participants (cross-sectional) and 222 (longitudinal subset).

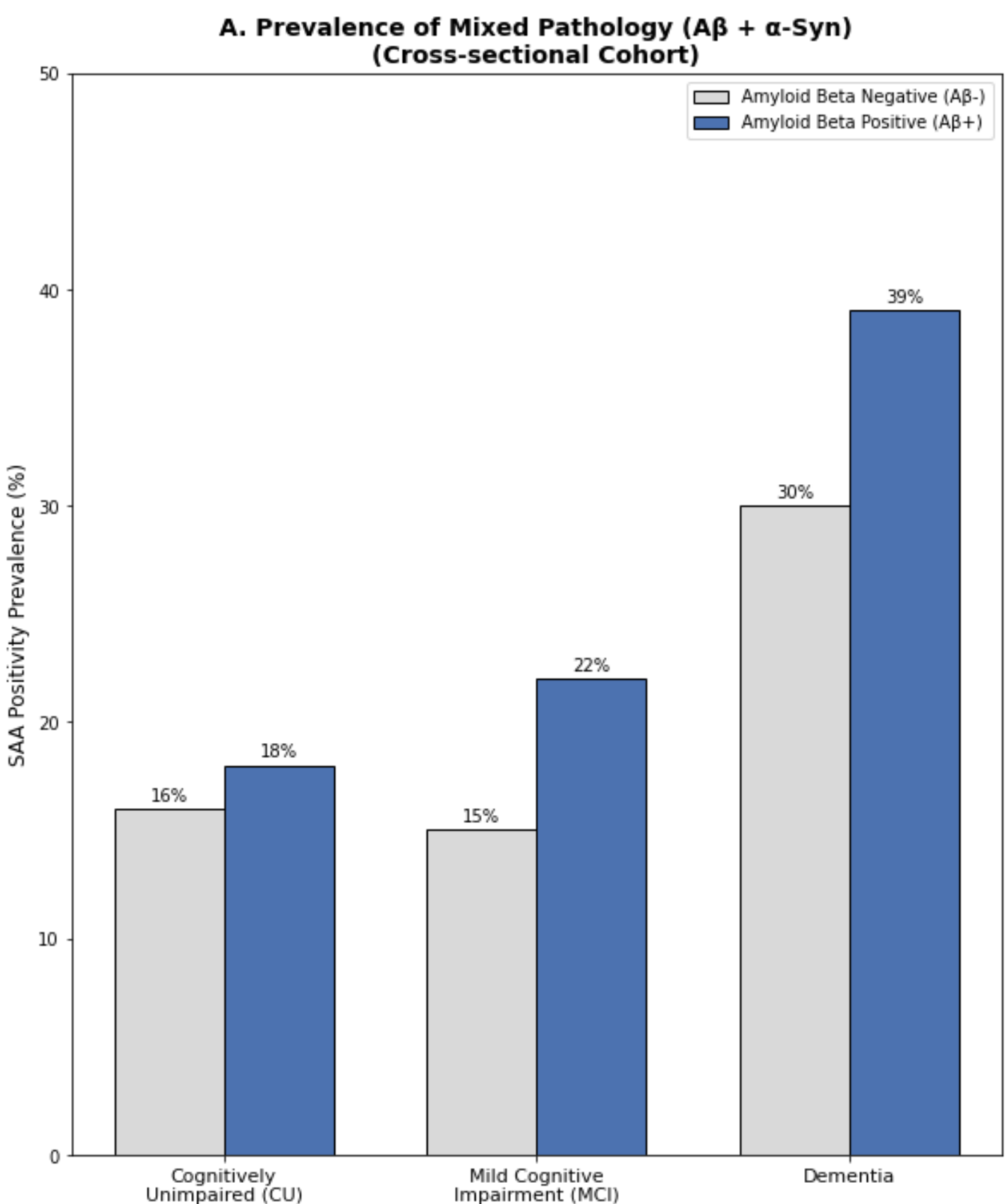
Assay Platform

Amprion α -syn SAA (SYNTap) using CSF samples.

Validation

Compared against autopsy-confirmed LB pathology (N=78) for diagnostic accuracy.

Analyses included AD biomarkers (CSF $A\beta$ 42, p -tau181) and APOE ϵ 4 genetics.

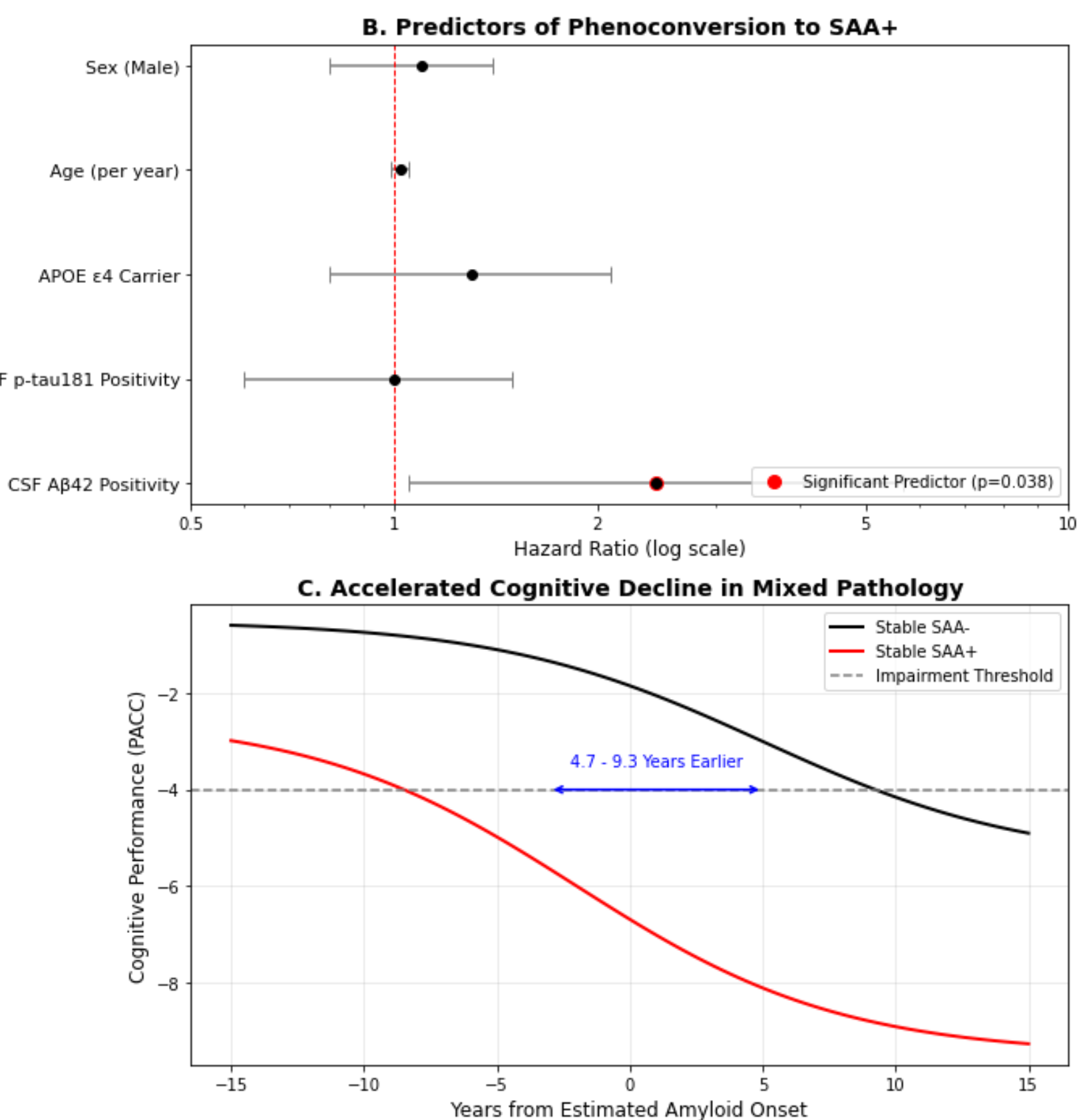


Prevalence of Mixed Pathology

SAA prevalence increased significantly with disease severity:

- ✓ 16% in Cognitively Unimpaired (CU)
- ✓ 19% in Mild Cognitive Impairment (MCI)
- ✓ 38% in Dementia

Amyloid positivity ($A\beta$ +) was associated with higher SAA+ rates across all stages.



Predictors of Phenoconversion

Survival analysis revealed a unidirectional crosstalk: Baseline CSF $A\beta$ 42 positivity significantly increased the risk of SAA phenoconversion (**Hazard Ratio: 2.44**). Notably, SAA status did *not* predict subsequent amyloid or tau positivity.

Accelerated Cognitive Decline

Presence of α -syn significantly accelerates disease progression. SAA+ individuals reach cognitive impairment thresholds **4.7–9.3 years earlier** than SAA– peers. Mixed pathology ($A\beta$ +/SAA+) drives faster decline in memory and executive function.

Conclusions

Mixed pathology is prevalent in AD and follows a specific temporal trajectory where amyloidosis appears to facilitate the emergence of α -synuclein co-pathology. The presence of α -syn significantly accelerates disease progression and lowers the age of symptom onset.

Clinical Trial Implications

Patient Stratification: Vital to account for SAA status in AD clinical trials to reduce outcome heterogeneity.

Trial Design: Mixed pathology patients follow a more aggressive trajectory; inclusion/exclusion based on SAA could improve signal detection.

Precision Medicine: Biomarker-driven diagnosis must consider the 20-30% overlap in pathology to provide accurate prognoses.