

Subjective Cognitive Decline Improves Prediction of Incident MCI Beyond AD Blood Biomarkers and Cognitive Measures

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BACKGROUND

- Alzheimer's disease (AD) blood biomarkers and cognitive measures are associated with clinical disease progression, but do not capture subjective cognitive decline (SCD).
- Questionnaires that capture SCD are scalable and low-cost and may provide complementary prognostic information for incident mild cognitive impairment (MCI).

OBJECTIVE

To determine whether SCD, cognitive screening, and AD blood biomarkers incrementally improve prediction of incident MCI among cognitively unimpaired older adults.

METHODS

Inclusion: Cognitively unimpaired participants from the MCSA and the combined A4 placebo/LEARN cohorts (Table 1).

SCD: Participant- and informant-reported ECog-12 in MCSA and participant- and informant-reported CFI in A4/LEARN.

Cognitive screening: MMSE.

Biomarkers: Plasma p-tau217 and GFAP.

Analyses: Cox models evaluated associations with incident MCI. Incremental prediction was assessed using nested models (Demographics → SCD → Cognitive measures → Biomarkers).

Discrimination was quantified with Uno's C-statistic.

TABLE 1: Overview of cohort characteristics.

	MCSA p-tau217 (n = 1107)	MCSA GFAP (n = 1572)	A4/LEARN (n = 1130)
Female sex			
n (%)	534 (48.2%)	753 (47.9%)	687 (60.8%)
Age (years)			
Mean (SD)	71.3 (8.2)	69.4 (10.3)	71.3 (4.7)
Incident MCI			
n (%)	102 (9.2%)	263 (16.7%)	281 (26.3%)
Concern			
n (%)	213 (19.5%)	331 (21.4%)	-
ECog-12/CFI score			
Mean (SD)	1.3 (0.3)	1.3 (0.3)	2.1 (2.0)
iECog-12/CFI-SP score			
Mean (SD)	1.2 (0.2)	1.1 (0.2)	1.2 (1.8)
MMSE score			
Mean (SD)	28.7 (1.1)	28.6 (1.2)	28.9 (1.2)
p-tau217 concentration (pg/mL)			
Mean (SD)	0.2 (0.1)	-	0.2 (0.1)
GFAP concentration (pg/mL)			
Mean (SD)	-	107.3 (66.0)	0.1 (0.1)

RESULTS

MCSA

- Participant-reported SCD (ECog-12 and concern) was associated with incident MCI (Figure 1).
- Informant-reported SCD (iECog) was also associated with incident MCI in the GFAP sample (Figure 1).
- Cognitive screening provided the largest incremental gain in discrimination, increasing C-statistics from 0.76–0.77 to 0.79–0.82.
- Adding plasma p-tau217 or GFAP only provided small additional gains (Δ C 0.00–0.01).

A4/LEARN

- Participant- (CFI) and informant-reported SCD (CFI-SP) were associated with incident MCI (Figure 2).
- Adding CFI improved model discrimination from 0.65 to 0.70.
- Plasma p-tau217 was strongly associated with incident MCI and improved discrimination: Δ C 0.06, $p < 0.0001$.

FIGURE 1: Variables associated with incident MCI in the MCSA

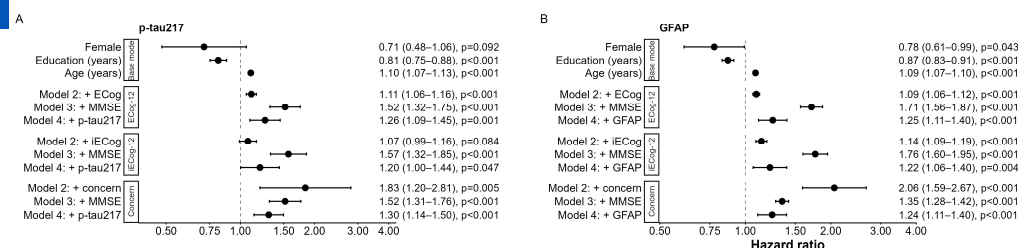
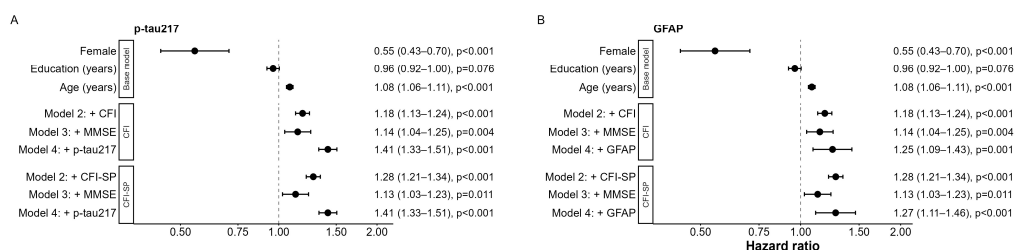


FIGURE 2: Variables associated with incident MCI in A4/LEARN



CONCLUSIONS

- SCD measures were consistently associated with incident MCI and provided modest incremental predictive value.
- These findings support risk-stratification approaches that begin with scalable SCD measures and selectively add cognitive screening and biomarkers by setting.