



Separate and Joint Effects of Stages of Objective Memory Impairment and Cognitive Function Index on Clinical Progression in A4

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OBJECTIVE

To determine whether prediction of incident clinical progression is enhanced by combining the Cognitive Function Inventory (CFI) and the Stages of Objective Memory Impairment (SOMI) system, compared to using either predictor alone with data from the Anti-Amyloid in Asymptomatic Alzheimer’s Disease (A4) study.

HYPOTHESIS

Combining **SOMI** and **CFI** enhances prediction of clinical progression compared to using either measure alone.

CONCLUSIONS

Subjective cognitive concerns and objective memory impairment separately and jointly predict progression in amyloid positive cognitively unimpaired individuals providing complementary information. Using both CFI and SOMI to determine eligibility for secondary prevention trials in amyloid positive individuals may improve trial efficiency.

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INTRODUCTION

- Only 20–30% of amyloid-positive cognitively normal individuals develop mild cognitive impairment (MCI) or clinical AD within 5 years.
- We sought to identify individuals at elevated risk of progression by combining objective and subjective measures of cognitive functioning.
- The SOMI system, defined by Free and Cued Selective Reminding Test scores, classifies increasing storage and retrieval deficits into 5 stages.
- Compared to participants with no memory impairment, those at

higher SOMI stages have a greater risk of progression.

- The CFI measures self-perceived cognitive decline by comparing current functioning to that of the previous year.
- CFI predicts clinical progression and tracts with the trajectory of cognitive decline over time.
- Using data from A4, we assessed the incremental predictive validity of combining SOMI and CFI, compared to models that included only one of these predictors.

METHODOLOGY

- 1,106 cognitively normal, amyloid-positive participants (baseline CDR = 0) were included, each with longitudinal FCSRT, CFI, and CDR data.
- Clinical progression was defined as the occurrence of two consecutive CDR scores greater than 0, over 4.5 years of follow-up.
- The CFI was dichotomized according to an optimal cut score determined through logistic regression with receiver operating characteristic (ROC) analysis.
- The 5 stages of the SOMI system were also grouped into participants

- whose memory was unimpaired (SOMI-0), subtle retrieval impairment (SOMI-1) versus those with immoderate to significant storage memory impairment (SOMI 2-4).
- Cox proportional hazards models, adjusted for age, sex, and APOE, were applied to examine the predictive value of CFI, SOMI, and their combination for incident clinical progression.
 - A partial likelihood ratio test between models assessed model improvement when the predictors were combined.

RESULTS

- Participants had a mean age of 71.9 years (SD = 4.8).
- At baseline, 38.6% were SOMI 0, and 61.4% were SOMI 1–4.
- 399 (36%) participants progressed, 707 (64%) did not during follow-up.
- The optimal CFI cut score = 2.58, yielding 67% accuracy in distinguishing progressors from non-progressors.
- In Cox models:
- High vs Low CFI: HR = 1.84 (95% CI: 1.51–2.24), $p < 0.001$.
- SOMI (ref = 0): SOMI 1 HR = 1.53 (1.16–2.01); SOMI 2–4 HR = 2.24 (1.71–2.94), p -values < 0.001 .
- Higher SOMI levels were associated with greater risk of progression.
- Both CFI and SOMI independently predicted progression
- Kaplan–Meier curves show joint contribution of CFI + SOMI in amyloid+ individuals

Table 2a: Cox Proportional Hazard Model Predicting Time to the Development of Incident Cognitive Impairment on Complete Dataset (Two consecutive CDR or last assessment CDR ≥0.5)

Term	HR	95% CI	p_val
With CFI			
CFI Self: High vs Low	1.84	1.51 - 2.24	< 0.001
age	1.06	1.04 - 1.08	< 0.001
Sex (Male)	1.32	1.08 - 1.61	0.007
APOE ε4+	1.25	1.02 - 1.54	0.033
With SOMI Stages			
SOMI: 1 vs 0	1.53	1.161 - 2.02	0.003
SOMI: 2/3/4 vs 0	2.24	1.71-2.94	< 0.001
age	1.06	1.04-1.08	< 0.001
Sex (Male)	1.22	0.99 - 1.50	0.07
APOE ε4+	1.26	1.02 - 1.56	0.031
With CFI + SOMI Stage			
CFI Self: High vs Low	1.82	1.49 - 2.24	< 0.001
SOMI: 1 vs 0	1.50	1.14 - 1.98	0.004
SOMI: 2/3/4 vs 0	2.22	1.69 - 2.91	< 0.001
age	1.05	1.03 - 1.08	< 0.001
Sex (Male)	1.20	0.97 - 1.48	0.09
APOE ε4+	1.22	0.98 - 1.50	0.072

Table 2b: Cox Proportional Hazard Model Predicting Time to the Development of Incident Cognitive Impairment on Dataset stratified by CFI-Self: CFI Low and CFI_Hgh (Two consecutive CDR or last assessment CDR ≥0.5)

Term	HR	95% CI	p_val
CFI - Low			
SOMI: 1 vs 0	1.86	1.27 - 2.73	0.001
SOMI: 2/3/4 vs 0	2.61	1.77 - 3.83	< 0.001
Age	1.07	1.04 - 1.11	< 0.001
Sex (Male)	1.18	0.88 - 1.58	0.262
APOE ε4+	1.27	0.95 - 1.70	0.104
CFI - High			
SOMI: 1 vs 0	1.15	0.77 - 1.71	0.508
SOMI: 2/3/4 vs 0	1.81	1.23 - 2.66	0.003
Age	1.03	1.002 - 1.07	0.034
Sex(Male)	1.26	0.92 - 1.72	0.146
APOE ε4+	1.16	0.85 - 1.59	0.353

Table 1. Baseline Characteristics of analysis population

	Stable (Event=0)	Progressors (Event=1)	Total
N	707	399	1106
Age (mean, SD)	71.35 (4.56)	72.99 (5.11)	71.94 (4.83)
Sex, Female	441 (62.4%)	208 (52.1%)	649 (58.7%)
APOE ε4+	406 (57.4%)	250 (62.7%)	656 (59.3%)
SOMI: 0 FR:>30, TR>46	290 (42.6%)	87 (23.2%)	377 (35.7%)
SOMI: 1 FR:25-30, TR>46	235 (34.5%)	130 (34.7%)	365 (34.6%)
SOMI: 2/3/4 SOMI 2: FR:20-24, TR>46 SOMI 3: FR: Any, TR: 45-46 SOMI 4: FR: Any, TR: 33-44	156 (22.9%)	158 (42.1%)	314 (29.7%)
CFI (Self): Low	512 (72.4%)	211 (52.9%)	723 (65.4%)
CFI (Self): High	195 (27.6%)	188 (47.1%)	383 (34.6%)
Amyloid SUVR (mean,SD)	1.30 (0.17)	1.38 (0.19)	1.33 (0.18)

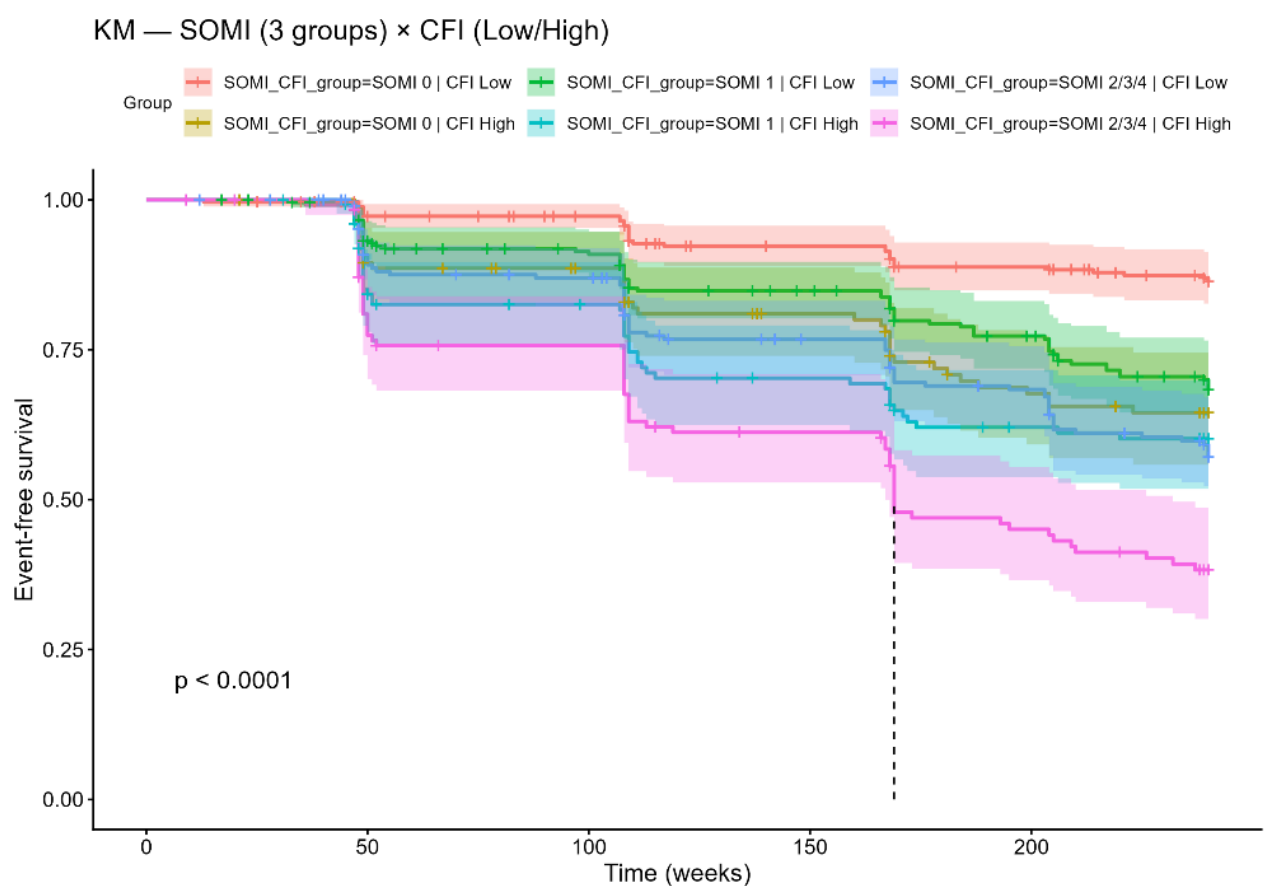


Figure: Kaplan Meir Curve for cognitive impairment free survival as a function of SOMI Stages and CFI