

Longitudinal Cognitive Decline Precedes Clinical Progression in Mild Cognitive Impairment: A Window For Intervention

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Cognitive decline precedes the first clinical progression from MCI to dementia.
Longitudinal monitoring of cognitive trajectories may identify individuals at imminent risk before CDR staging changes, expanding opportunities for earlier intervention.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS																			
• Clinical Dementia Rating (CDR) is widely used to identify progression from mild cognitive impairment (MCI) to dementia. • Although cognitive impairment predicts future dementia, it remains unclear whether measurable cognitive decline precedes the first observed increase in CDR. • We investigated longitudinal cognitive trajectories before clinical transition to determine whether cognitive decline provides an earlier marker of disease progression.	Study Design: Longitudinal Observational study •Data source: Mayo Clinic Study of Aging (MCSA) •Participants: 487 individuals with MCI (baseline CDR = 0.5) and ≥2 follow-up visits •Clinical outcomes: Progressed to dementia (first CDR ≥1, <i>n</i>=105) or reverted to normal cognition (first CDR = 0, <i>n</i>=223) •Cognitive measures: Standardized global and domain-specific cognitive z-scores •Analysis: Cognitive trajectories were aligned to the first CDR transition, and pre-transition cognitive slopes were compared between outcome groups	<table><tr><th>Baseline Characteristics</th><th>Progressed (n = 105)</th><th>Reverted (n = 223)</th></tr><tr><td>Age, years*</td><td>79.5 ± 4.4</td><td>70.9 ± 11.4</td></tr><tr><td>APOE ε4 carriers, %*</td><td>52.4</td><td>30.4</td></tr><tr><td>Global cognition (z-score)*</td><td>-2.34</td><td>-1.06</td></tr><tr><td>Memory (z-score)*</td><td>-2.37</td><td>-1.12</td></tr><tr><td>High-intensity physical activity†</td><td>5.0 [1.5–9.0]</td><td>7.0 [3.5–12.5]</td></tr></table> Progressors were older, more frequently APOE ε4 carriers, and had worse baseline global cognition and memory. Reverters reported higher levels of high-intensity physical activity. (* <i>p</i>-value<0.001)	Baseline Characteristics	Progressed (n = 105)	Reverted (n = 223)	Age, years*	79.5 ± 4.4	70.9 ± 11.4	APOE ε4 carriers, %*	52.4	30.4	Global cognition (z-score)*	-2.34	-1.06	Memory (z-score)*	-2.37	-1.12	High-intensity physical activity†	5.0 [1.5–9.0]	7.0 [3.5–12.5]	Pre-transition slope of global cognitive z-score Progressed (n=105) Reverted (n=223) <i>p</i> < 0.001 • The median time from baseline MCI to first CDR increase was 3.8 years. • Progressors demonstrated significantly greater pre-transition decline in global cognition than reverters (−0.24 vs near-zero SD/year; <i>p</i> < 0.001). • Memory decline also preceded clinical progression, whereas cognitive improvement was not observed before reversion.	•Global cognitive decline and memory impairment preceded the first clinical progression from MCI to dementia. •Longitudinal cognitive monitoring may identify individuals at imminent risk before changes in CDR become clinically apparent. •These findings support longitudinal cognitive trajectories as a potential tool for earlier intervention.
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