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Determining clinically meaningful decline in preclinical Alzheimer disease

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Study objective and summary result

This study aimed to determine the time required for clinically meaningful cognitive decline in patients with preclinical Alzheimer disease (AD). Amyloid β (Aβ)-positive patients with normal cognition approached levels of performance typically associated with mild cognitive impairment 6 years after baseline.

What is known and what this paper adds

To effectively alter AD outcomes, targeted interventions may be needed during the preclinical stage. Insight into an appropriate definition for "meaningful decline" is provided, which may help to identify the optimal treatment window for patients with AD.

Participants and setting

The study included 443 cognitively healthy controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI); 348 from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study; and 329 from the BioFINDER study, in addition to 305 participants of the early MCI ADNI cohort for comparative analysis.

Design, size, and duration

Aβ status was evaluated via PET or CSF biomarkers. Neuropsychological tests were conducted over a follow-up period of up to 6 years. The mean time was evaluated for the average patient with preclinical AD to achieve the mean baseline Preclinical Alzheimer's Cognitive Composite (PACC) score observed in the early MCI group.

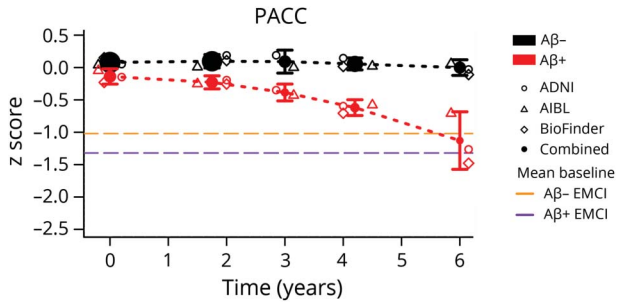
Primary outcome measures

PACC total and component scores were regarded as the primary outcome measure.

Main results and the role of chance

Patients with preclinical AD exhibited performance similar to that observed in MCI populations after 6 years of follow-up. A total of 2,000 participants per group are required to achieve 80% power in a simulated 4-year trial with an assumed treatment effect of 25%, while 600 participants are required for a 6-year trial. Although various factors interacted with Aβ status to influence cognitive decline, the findings were cohort-specific.

Figure Meta-estimates of change over time shown by Aβ group and individual cohort estimates



The mean baseline early MCI scores are shown in dashed purple for Aβ+ and dashed orange for Aβ−.

Bias, confounding, and other reasons for caution

Variations existed in the measures used to develop the PACC score in each cohort. The drug effect was speculative, though if the drug effect was assumed, there was adequate power to detect it.

Generalizability to other populations

Given the strict exclusionary criteria, participants had few comorbidities and did not mirror the general population, limiting the generalizability of the findings.

Study funding/potential competing interests

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A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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