Plasma Aβ42Aβ40 determined by mass spectrometry is associated with longitudinal changes in amyloid accumulation, brain atrophy, and conversion to mild cognitive impairment due to Alzheimer's disease in individuals with subjective cognitive decline 5-year follow-up of the FACEHBI cohort

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Abstract:

Background: The accurate identification of individuals at risk of Alzheimer's disease (AD) through blood-based biomarkers remains challenging.

Objectives: To evaluate the association between plasma amyloid-beta (Aβ)42/Aβ40 ratio and longitudinal amyloid deposition, clinical progression, brain atrophy and cognitive decline.

Design, setting and participants: This study extends the Fundació ACE Healthy Brain Initiative (FACEHBI) study (Barcelona, Spain), comprising 200 individuals with subjective cognitive decline (SCD) followed over five years.

Measurements: Aβ42/Aβ40 ratio was quantified using ABtest-MS, an antibody-free mass-spectrometry (MS) method. Survival analyses compared conversion risks to amyloid-PET positivity and mild cognitive impairment (MCI), in participants classified as low or high Aβ42/Aβ40, based on a cutoff of ≤ 0.241. Linear mixed-effect models evaluated associations of this biomarker with longitudinal changes in amyloid deposition, brain volume, and cognition.

Results: Low baseline Aβ42/Aβ40 was significantly associated with increased amyloid accumulation (β = 0.257, 95% confidence interval (CI) 0.177-0.336, P < 0.001), and with higher risk of conversion to Aβ-PET positivity (Hazard ratio (HR) = 2.84, 95% CI 1.14-7.04, P = 0.025) and to MCI due to AD (HR = 3.25, 95% CI 1.17-9.01, P = 0.024). It was also linked to decreased hippocampal (β = -1.183, 95% CI -2.154 to -0.211, P = 0.017) and cortical (β = -75.921, 95% CI -151.728 to -0.113, P = 0.050) volumes, and increased ventricular volume (β = 35.175, 95% CI 18.559-51.790, P < 0.001). Moreover, lower baseline levels of Aβ42/Aβ40 were weakly associated with greater worsening in Mini-Mental State Examination and complex associative memory.

Conclusions: Our findings suggest that the plasma Aβ42/Aβ40 ratio is associated with future amyloid accumulation, brain atrophy, and conversion to prodromal AD in individuals with SCD. This biomarker may help characterize individuals with a higher likelihood of progression and could support earlier and more personalized strategies.

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