

AD Biomarkers Linked to Worse Cognition in Midlife Adults

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The identification of Alzheimer's disease (AD) pathology typically occurs late in the disease course, often after significant neurodegeneration and cognitive decline have manifested. However, emerging evidence suggests that the biological changes associated with AD, specifically the accumulation of amyloid-beta (A β) and tau proteins, begin decades before clinical symptoms appear. Understanding the impact of these preclinical biomarkers on cognitive function in midlife adults is critical for identifying individuals at higher risk and potentially informing early intervention strategies.

KEY TAKEAWAYS

- **The Pivot:** AD biomarkers, previously studied predominantly in older populations, are now being assessed for their cognitive impact in midlife.
- **The Data:** Elevated A β and tau levels in cerebrospinal fluid (CSF) or via PET imaging are associated with measurable, albeit subtle, decrements in specific cognitive domains in individuals aged 40-65 years.
- **The Action:** Clinicians should be aware that AD pathology can manifest cognitively in midlife, prompting consideration of biomarker assessment in at-risk individuals, though current interventions remain limited.

Alzheimer's disease is characterised by the progressive accumulation of amyloid-beta (A β) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological hallmarks are detectable in cerebrospinal fluid (CSF) and through positron emission tomography (PET) imaging years, even decades, before the onset of symptomatic dementia.¹ The presence of these biomarkers in asymptomatic individuals is considered indicative of preclinical AD.² While the relationship between these biomarkers and cognitive decline is well-established in older adults, their association with cognitive performance in midlife (typically defined as ages 40-65 years) has been a focus of recent investigation.³ This period is critical for understanding the earliest manifestations of AD pathology, as interventions initiated during midlife may have a greater potential to delay or prevent the progression to symptomatic dementia. The identification of subtle cognitive changes in midlife adults with preclinical AD could therefore inform targeted prevention strategies and identify individuals at higher risk for future cognitive decline. Understanding the trajectory of these changes is crucial for developing effective early detection and intervention paradigms.

What the study did

Studies investigating AD biomarkers in midlife adults typically employ cross-sectional or longitudinal designs to assess the relationship between biomarker status and cognitive function. Participants are often recruited from large population-based cohorts or memory clinics, with careful exclusion of individuals with overt dementia or other

neurological conditions that could confound cognitive assessment.⁴ Recruitment strategies often involve community outreach and collaborations with primary care providers to ensure a representative sample of cognitively normal midlife adults. Biomarker assessment commonly involves CSF analysis for A β 2, total tau (t-tau), and phosphorylated tau (p-tau), or PET imaging using tracers such as florbetapir (for A β 3) and flortaucipir (for tau).⁵ Blood-based biomarkers, including plasma A β 2/40 ratio and p-tau isoforms, are also emerging as less invasive alternatives for screening and monitoring. Cognitive function is evaluated using comprehensive neuropsychological batteries, assessing domains including memory, executive function, processing speed, and language.⁶ These batteries often include tests such as the Rey Auditory Verbal Learning Test for episodic memory, the Trail Making Test for executive function and processing speed, and the Boston Naming Test for language.

A consistent finding across multiple cohorts is that midlife adults with evidence of AD pathology, such as reduced CSF A β 2 or elevated amyloid PET signal, exhibit poorer performance on specific cognitive tests compared to biomarker-negative individuals.⁷ For instance, a study of N=300 cognitively normal adults (mean age 55 years) found that those with amyloid positivity on PET imaging demonstrated significantly lower scores on tests of episodic memory (P=0.003) and executive function (P=0.012) compared to amyloid-negative controls.⁸ Similarly, elevated CSF p-tau levels in midlife have been associated with slower processing speed (P=0.008) and reduced verbal fluency (P=0.021).⁹ These cognitive differences, while statistically significant, are often subtle and may not meet criteria for mild cognitive impairment (MCI).¹⁰ Longitudinal studies have further indicated that midlife individuals with preclinical AD biomarkers show a faster rate of cognitive decline over several years compared to those without such biomarkers.¹¹ For example, a 5-year follow-up of N=250 individuals (mean age 58 years at baseline) revealed that those with elevated CSF t-tau experienced a greater annual decline in global cognitive scores (P=0.001) and memory composite scores (P=0.002).¹² The mechanisms underlying these early cognitive changes are thought to involve synaptic dysfunction and early neuronal injury preceding widespread neurodegeneration.

Limitations of current research include the relatively small sample sizes in some cohorts, particularly for longitudinal studies, and the heterogeneity in biomarker definitions and cognitive assessment tools across different investigations.¹³ The clinical significance of these subtle cognitive differences in midlife remains a subject of ongoing debate, as not all individuals with preclinical AD biomarkers will progress to symptomatic dementia within their lifetime.¹⁴ Furthermore, the influence of confounding factors such as vascular risk factors, psychiatric comorbidities, and educational attainment on cognitive performance in midlife adults with AD biomarkers requires further elucidation. The generalizability of findings from highly selected research cohorts to the broader midlife population also warrants careful consideration. Future research needs to focus on larger, more diverse cohorts and standardise methodologies to better characterise the trajectory of cognitive change in midlife individuals with AD pathology. The development of more sensitive cognitive measures capable of detecting subtle changes earlier in the disease process is also essential.¹⁵ This includes the exploration of digital cognitive assessments and ecological momentary assessment to capture real-world cognitive performance.

CLINICAL IMPLICATIONS

The increasing evidence that Alzheimer's disease pathology manifests cognitively in midlife presents a complex challenge for general practitioners and specialists. While the data consistently link elevated AD

biomarkers to measurable decrements in cognitive performance, these changes are often subclinical. This raises the question of when, and for whom, biomarker testing becomes clinically relevant. Currently, there are no disease-modifying therapies approved for preclinical AD, meaning a positive biomarker result in an asymptomatic midlife adult offers limited immediate therapeutic recourse. This situation risks creating anxiety without a clear path to intervention.

For clinicians, the current landscape necessitates a cautious approach. Routine screening for AD biomarkers in asymptomatic midlife adults is not yet supported by clinical guidelines, given the lack of effective interventions and the potential for psychological distress. However, for individuals with a strong family history of early-onset AD or those presenting with subjective cognitive concerns that warrant further investigation, biomarker assessment might be considered within a research context or specialised memory clinic. The pharmaceutical industry continues to invest heavily in therapies targeting amyloid and tau, with trials exploring their efficacy in earlier disease stages. Should these trials yield positive results, the utility of midlife biomarker detection would dramatically increase, potentially shifting the paradigm towards preventative or early disease-modifying treatment.

Patients, particularly those with a genetic predisposition or a heightened awareness of AD risk, may increasingly seek biomarker testing. It is imperative that clinicians provide comprehensive counselling, explaining the implications of a positive result, the current absence of definitive treatments for preclinical AD, and the potential for psychological impact. The focus should remain on modifiable risk factors for cognitive decline, such as managing hypertension, diabetes, and promoting physical activity and cognitive engagement, which offer tangible benefits regardless of biomarker status. Until effective early interventions are available, the primary utility of midlife AD biomarker research remains in advancing our understanding of disease progression and identifying populations for future clinical trials, rather than guiding immediate clinical practice for the general population.

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