

Peripheral TNF-A-Driven Inflammation & Its Effect On Cognition In Alzheimer's Disease (AD) Adjuvant Therapies



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BACKGROUND

Tumor necrosis factor-alpha (TNF- α) plays a central role in neuroinflammation and has been associated with Alzheimer's disease (AD) progression.

Although individual studies suggest links between TNF- α levels and cognitive decline, the relationship remains uncertain. To address this gap, the present review correlates plasma TNF- α with cognition in clinical trials targeting AD.

METHODS

Following **PRISMA 2020 guidelines** and a prospective registration in PROSPERO (CRD42025345678), CENTRAL, Medline, Scopus, Web of Science, and MedRxiv were searched (up to November 2025).

Dual screening was performed, with disagreements resolved through consensus. For each eligible randomized controlled trial (RCT) reporting longitudinal plasma TNF- α alongside cognition (MMSE, ADAS-Cog, MoCA, TYM), data extraction and risk-of-bias assessment were performed.

Outcomes were Z-standardized, and correlations between TNF- α and cognitive changes explored by meta-regression (REML, Knapp-Hartung).

KEY FINDINGS

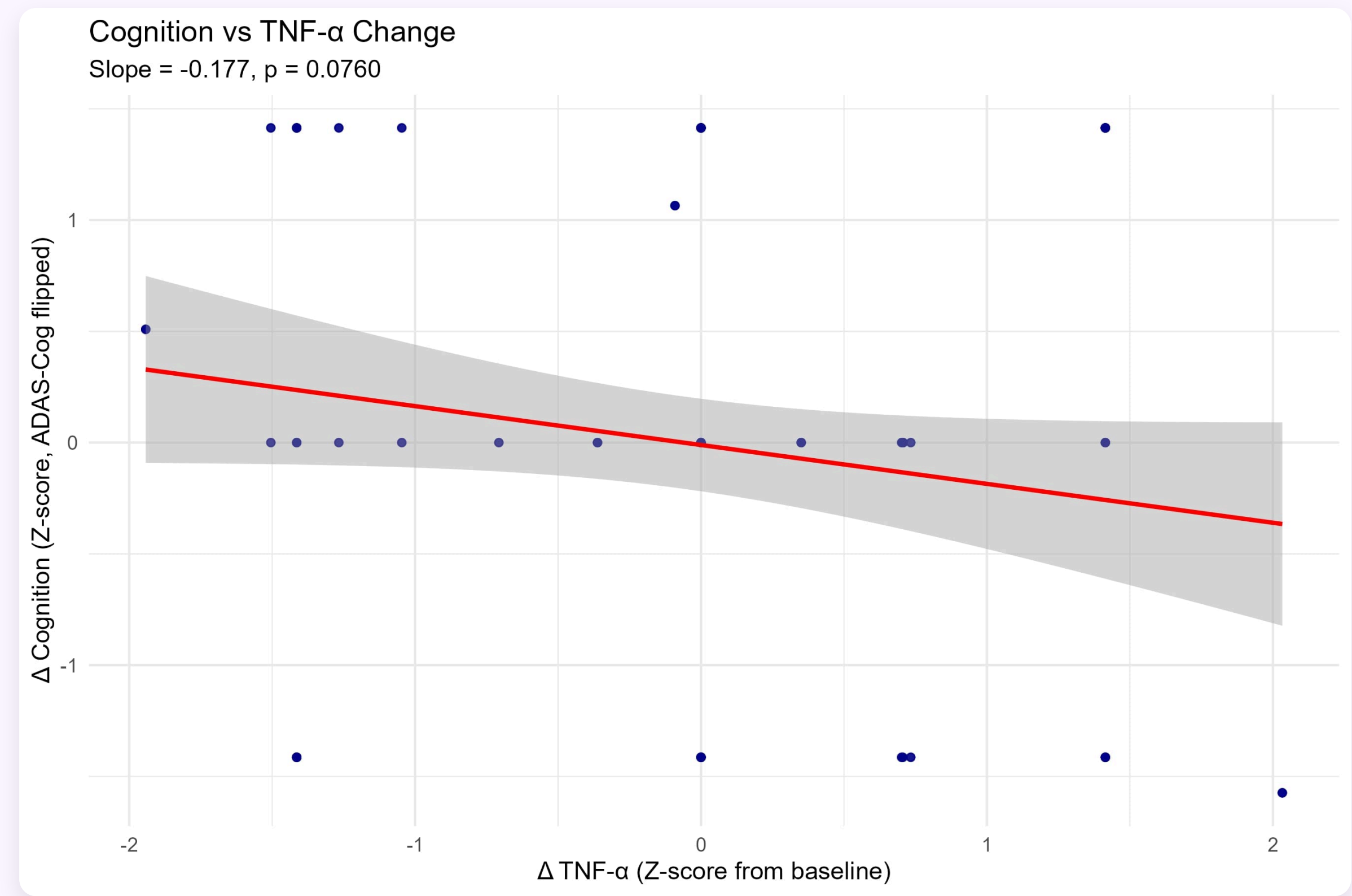


Figure 1: Meta-regression Scatter Plot mapping changes in TNF- α to Cognition

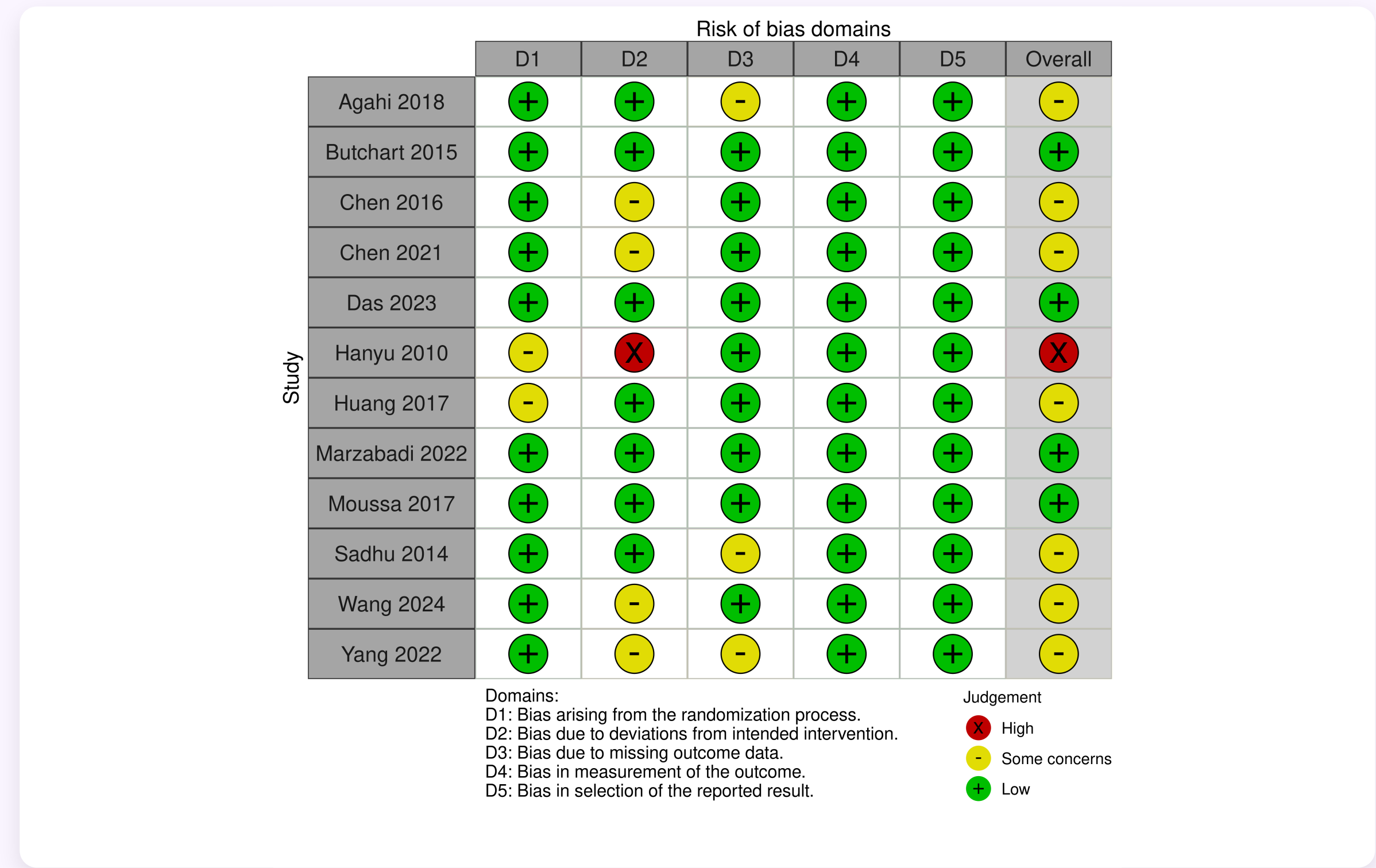


Figure 2: Risk of Bias Assessment

RESULTS

Twelve RCTs enrolling **1067 participants** were retrieved, judged moderate risk of bias, in which TNF- α changes were marginally related to cognition.

A -1 SD change in TNF- α represented a **-0.177 SD change in cognition** (β = -0.177, 95% CI -0.373 to 0.019, p = 0.076), with no evidence for lead/lag relationships or interaction effects by intervention class, duration, or patient variables (age, sex, severity, APOE4).

High residual heterogeneity (I^2 = 94.9%) did not affect sensitivity analyses, with minimal publication bias (Egger's t = -0.825, p = 0.411) and diagnostics supporting robustness.

CONCLUSIONS

This meta-correlation establishes a **modest, marginally significant relationship** between TNF- α reduction in AD trials and cognitive improvement.

These findings underscore the importance of inflammatory pathway modulation and the urgent need for biomarker-dense, extended clinical trials in Alzheimer's disease research.