

Plasma Phosphorylated Tau 217 and Amyloid-β 42/40 Are Associated With Minimal Depressive Symptoms in Alzheimer's Disease

AAIC
2026

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KEY TAKEAWAY: Minimal depressive symptoms were linked to higher plasma p-Tau217 and lower Aβ42/Aβ40; p-Tau217 mediated ~42% of the MDS-cognition association.

INTRODUCTION

Background

- Depressive symptoms are a recognized risk factor and potential prodromal feature of Alzheimer's disease (AD).
- CSF and PET studies link depression to amyloid and tau pathology, but plasma-based evidence remains less defined.

Objective

- To determine whether minimal depressive symptoms (MDS) are associated with plasma AD biomarkers and cognitive impairment.
- To test whether plasma biomarkers mediate the relationship between MDS and cognition.

Hypothesis

- Accessible plasma p-Tau217 and Aβ42/Aβ40 may capture an AD-core pathological pathway connecting early depressive symptoms to cognitive decline.

METHODS

Study population

- ADNI cohort: 615 participants; 374 had MDS.
- Analyses focused on the full cohort and non-demented individuals.

Plasma biomarkers

- p-Tau217, Aβ42/Aβ40 ratio, NfL and GFAP.

Cognitive outcomes

- MMSE and ADAS13 as measures of global cognition and AD-related cognitive impairment.

Statistics

- Linear regression and FDR correction assessed MDS-biomarker/cognition associations.
- Mediation models estimated the indirect effects of p-Tau217 and Aβ42/Aβ40.
- Models adjusted for age, sex and APOE ε4 carrier status; subgroup analyses tested effect modification.

RESULTS

MDS was associated with an AD-core plasma biomarker profile.

Main findings

- p-Tau217 was higher in MDS: mean difference = 0.105, $P < 0.001$.
- Aβ42/Aβ40 was lower in MDS: mean difference = -0.024, $P = 0.007$.
- NfL and GFAP were not significantly associated with MDS.

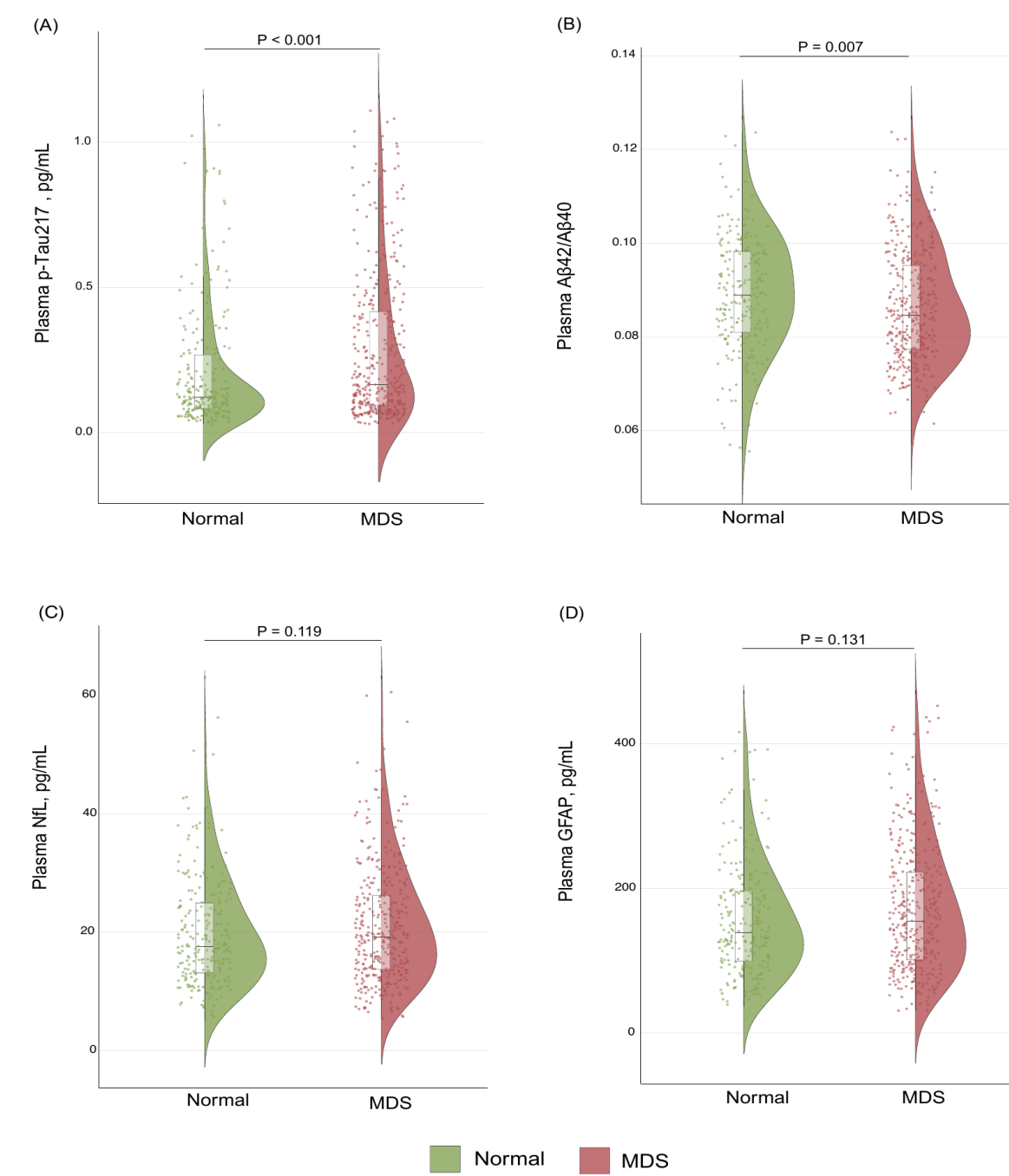


Figure 1. Group differences in plasma p-Tau217, Aβ42/Aβ40, NfL and GFAP.

RESULTS

Associations were modified by age, sex and APOE ε4 status.

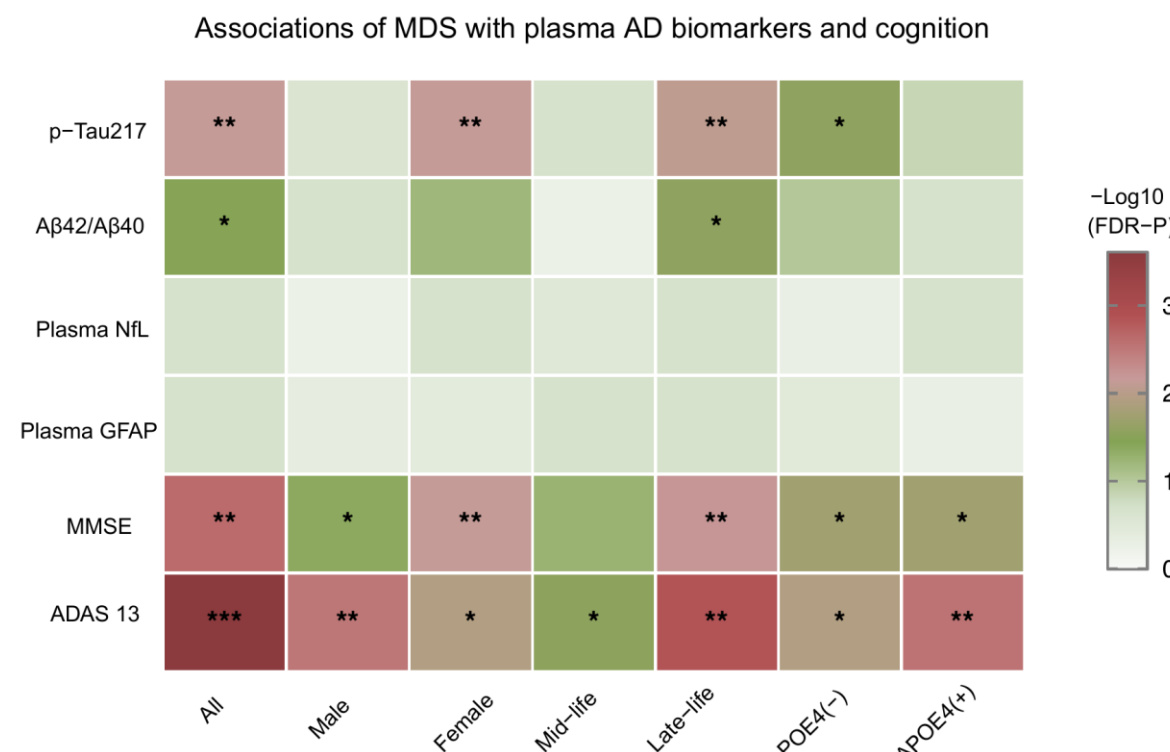


Figure 2. Heatmap of MDS associations across subgroups.

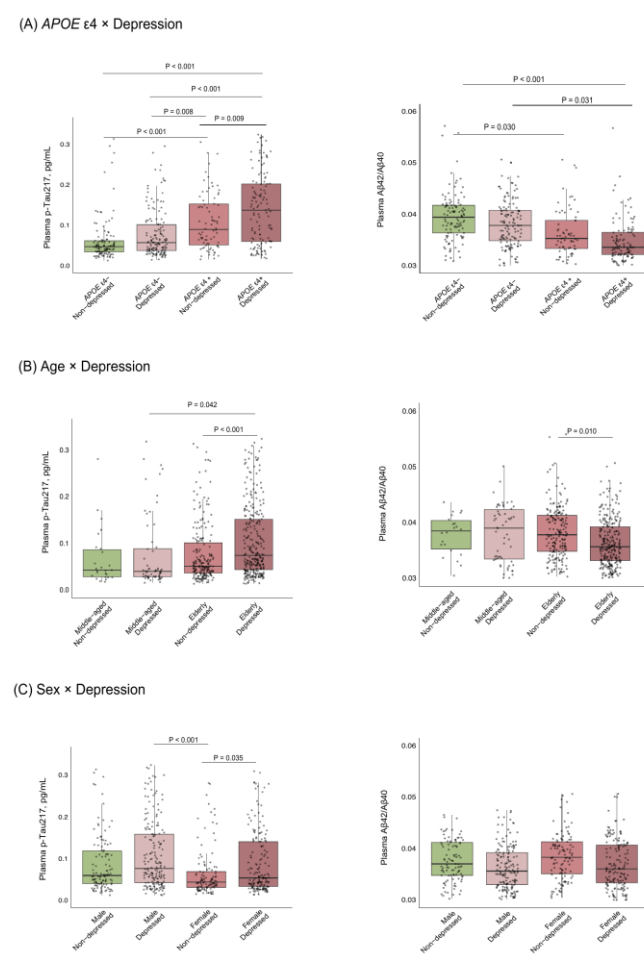


Figure 3. APOE ε4-, age- and sex-stratified biomarker patterns.

CONCLUSIONS

In conclusion, plasma p-Tau217 and Aβ42/Aβ40 were associated with MDS and accounted for part of the association between these symptoms and cognitive impairment. These findings identify plasma p-Tau217 as a key mediator linking MDS to impaired cognition, extending evidence from CSF to accessible blood-based biomarkers. They underscore the value of monitoring plasma p-Tau217 and Aβ42/Aβ40 to elucidate the pathological basis of depressive symptoms in early AD.

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