

Plasma Biomarkers And Neuropsychiatric Symptoms In Cognitively Unimpaired Older Adults: A Systematic Review.

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Neuropsychiatric symptoms (NPS) and Mild Behavioral Impairment (MBI) are increasingly recognized as non-cognitive manifestations of the preclinical Alzheimer’s disease (AD) continuum. While the AT(N) framework has validated plasma biomarkers (p-tau, amyloid-β, neurofilament light [NfL], and glial fibrillary acidic protein [GFAP]) for cognitive decline, the biological substrates underlying specific behavioral phenotypes in cognitively unimpaired(CU) individuals remain incompletely characterized. Existing studies report heterogeneous and sometimes conflicting associations between plasma biomarkers and NPS. This systematic review aimed to synthesize recent evidence linking distinct plasma biomarkers to specific NPS domains in preclinical populations.	A systematic review was conducted using PubMed/MEDLINE, Web of Science, and Embase databases. They were searched for observational studies published between January 2020 and January 2026. Inclusion criteria were: (1) cohorts of CU older adults, individuals with subjective cognitive decline, or early prodromal AD; (2) quantification of plasma biomarkers (p-tau181/217, amyloid-β42/40, NfL, or GFAP); and (3) assessment of NPS using validated instruments. Due to methodological heterogeneity across studies, findings were synthesized qualitatively, focusing on directionality and domain-specific associations.	The search identified 334 records, of which four studies met the predefined inclusion criteria. Ghahremani et al. (2022; n=571) reported a significant association between elevated plasmap-tau 181 and total MBI scores (β=8.1%, p=0.02), suggesting a link between MBI and early tau pathology. In contrast, Huang et al. (2023) observed no significant association between plasmap-tau and NPS; instead, plasma NfL was associated with anxiety and psychosis (OR=1.02,p=0.04), consistent with generalized axonal degeneration. Wei et al. (2024) provided preliminary evidence that depressive symptoms in CU individuals (n=82) were associated with plasma amyloid-β42/40 ratios (r=0.45, p=0.03). Finally, Ikanga et al. (2025) found that plasma GFAP was strongly associated with irritability (OR=3.34, p=0.01) in early, preclinical stages.	Neuropsychiatric symptoms in preclinical AD reflect distinct underlying biological processes rather than a unified mechanism. While MBI appears preferentially associated with tau pathology, depressive symptoms show associations with amyloid burden, whereas psychosis and irritability are more closely linked to neurodegeneration and neuroinflammation, respectively. These findings support a precision neuropsychiatry approach in which plasma biomarker profiles may aid in stratifying neuropsychiatric risk prior to overt cognitive decline.	1. Ghahremani M, Wang M, Chen HY, et al. Plasma Phosphorylated Tau at Threonine 181 and Neuropsychiatric Symptoms in Preclinical and Prodromal Alzheimer Disease. <i>Neurology</i>. 2022;99(20):e2220-e2230. 2. Huang L, Huang Q, Xie F, Guo Q. Neuropsychiatric symptoms in Alzheimer's continuum and their association with plasma biomarkers. <i>J Affect Disord</i>. 2023;349:330-337. 3. Wei YC, Kung YC, Lin C, et al. Differential neuropsychiatric associations of plasma biomarkers in older adults with major depression and subjective cognitive decline. <i>Transl Psychiatry</i>. 2024;14(1):335. 4. Ikanga J, Patel SS, Schwinne M, et al. Association between neuropsychiatric symptoms and neurodegeneration-related plasma biomarkers in older adults with and without clinical dementia in the Democratic Republic of the Congo. <i>Alzheimers Dement</i>. 2025; Epub ahead of print. CONTACT gabriellemaia0804@gmail.com ALZHEIMER'S ASSOCIATION AAIC>26