

From malnutrition to neuropsychiatric symptoms in Alzheimer's disease: sequential mediating effect by plasma P-tau217 and cognitive impairment

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In AD patients, malnutrition indirectly exacerbates neuropsychiatric symptoms through a sequential pathway involving elevated plasma P-tau217 and subsequent cognitive decline, with mediation effects accounting for 50.6% of the total effect on overall neuropsychiatric symptoms and 57.4% on agitation.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS
To elucidate the pathophysiological mechanisms underlying Alzheimer's disease (AD) with malnutrition (AD-M) and the role of plasma AD biomarkers in linking malnutrition to cognition and neuropsychiatric symptoms.	Total 182 participants, including AD-M (n=84) and AD with no malnutrition (AD-nM, n=98), were enrolled. Nutritional status was assessed using the Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria and Mini Nutritional Assessment (MNA) scale. Clinical symptoms were evaluated by various rating scales. Plasma and cerebrospinal fluid (CSF) AD biomarkers were measured by immunoassay. Multiple regression and Bootstrap mediation analyses were performed.	(1) Compared with AD-nM group, AD-M group showed lower scores of Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Auditory Verbal Learning Test (AVLT), Rey-Osterrieth Complex Figure Test (RCFT) delayed recall, Verbal Fluency Test (VFT), Boston Naming Test (BNT), Trail Making Test (TMT)-A, Stroop Color Word Test (SCWT)-A, SCWT-B, SCWT-C and TMT-B (all P < 0.05); AD-M group had higher scores of Neuropsychiatric Inventory (NPI) and Cohen-Mansfield Agitation Inventory (CMAI) (all P < 0.05). (2) After adjusting for confounding factors, malnutrition in AD patients remained independently associated with lower scores of MMSE, MoCA, AVLT (N1–N3), VFT, BNT, TMT-A, TMT-B, SCWT-B and SCWT-C scales. Malnutrition was independently associated with higher scores of NPI and CMAI (all P < 0.05).	(3) Malnutrition was independently associated with elevated plasma P-tau217, P-tau217/Aβ42, P-tau181 and P-tau181/Aβ(42/40) levels, decreased CSF Aβ42 level, and increased CSF T-tau/Aβ42, P-tau181, P-tau181/Aβ42 and P-tau231 levels (all P < 0.05). (4) Parallel mediation analysis revealed that elevated plasma P-tau217 level partially mediated the relationship between malnutrition and overall cognition (34.8%), memory (30.9%), language (30.9%), attention (24.0%), and executive function (33.3%). (5) Serial mediation analysis uncovered that malnutrition indirectly aggravated overall neuropsychiatric symptoms (50.6%) and agitation (57.4%) via elevated plasma P-tau217 level and subsequent cognitive decline.	Malnutrition is an independent risk factor for cognitive impairments and neuropsychiatric symptoms in AD, aggravates cerebral Aβ and tau pathology. Malnutrition indirectly exacerbates neuropsychiatric symptoms through a sequential pathway involving elevated plasma P-tau217 and subsequent cognitive impairment. CONTACT ttyyzw@163.com Center for Cognitive Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing,100070, China. 