

Background

- Neuropsychiatric symptoms (e.g., apathy, depression, anxiety, agitation, disinhibition, psychosis) have conventionally been thought to emerge in later clinical stages of Alzheimer’s disease (AD) such as dementia.¹
- There is growing evidence that neuropsychiatric symptoms meeting mild behavioural impairment (MBI) criteria (i.e., later life emergence and persistence) may emerge in AD well before dementia.²

Objective

To examine whether older adults with biomarker-defined AD are: 1) more likely to exhibit MBI; and 2) more likely to develop MBI over time.

Methods

- n=970 (51.4% female; 76.3% White) participants aged 73.7±8.0 years from the ADNI study³
- 62.7% cognitively unimpaired (CU)
- 35.4% mild cognitive impairment (MCI)
- Aβ42, Aβ40, and p-tau217 were measured using the Fujirebio Lumipulse G1200 platform; NfL and GFAP using Neurology 2-Plex kits on the Simoa Quanterix HD-X platform.
- Biomarker-defined AD status determined based on cutpoints recommended by the ADNI Biomarker Core:⁴
- (-) p-tau217: ≤0.128 pg/mL; (-) p-tau217/Aβ42: ≤0.0055
- (+) p-tau217: ≥0.300 pg/mL; (+) p-tau217/Aβ42: ≥0.1053
- Participants in between lower and upper cutoffs were considered intermediate.
- MBI status was determined based on presence of MBI symptoms, measured using the Neuropsychiatric Inventory (NPI) or NPI Questionnaire that were retrospectively identified as persistent across ≥2/3 of dementia-free visits.⁵
- The association between AD status (exposure) and MBI (outcome) was modelled using logistic and Cox proportional hazards regression models.
- Adjusting for age, sex, years of education, APOE e4 carrier status, and ADAS-Cog.

Conclusion

- Older adults with biomarker-defined AD are more likely to exhibit and are at greater risk of developing neuropsychiatric symptoms consistent with MBI criteria prior to dementia.
- These findings support the inclusion of MBI in early AD clinical staging frameworks and warrant consideration in the diagnostic work-up of AD.

Behavioural manifestations in biomarker-defined Alzheimer’s disease before dementia

Evidence for mild behavioural impairment in biomarker-defined Alzheimer’s disease: An ADNI study

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Table 1. Cross-sectional associations between biomarkers and odds of MBI

Exposure	OR	95% CI	p
p-tau217/Aβ42			
Positive	1.70	1.15, 2.52	.008/.01
Intermediate	1.12	0.71, 1.78	.62
Continuous (SD)	1.20	1.03, 1.39	.02
p-tau217			
Positive	1.92	1.23, 3.00	.004/.01
Intermediate	1.13	0.76, 1.69	.54
Continuous (SD)	1.23	1.06, 1.44	.008
NfL (continuous; SD)	1.35	1.13, 1.62	.001
GFAP (continuous; SD)	1.21	1.01, 1.44	.04
p-tau217/Aβ42			
Positive	1.70	1.15, 2.52	.008/.01
Intermediate	1.12	0.71, 1.78	.62

All estimates are derived from multivariable logistic regression models with MBI status as the outcome variable, adjusted for age, sex, years of education, APOE e4 carrier status, and ADAS-Cog. ORs should be interpreted as the expected relative difference in odds of MBI between biomarker positive versus biomarker negative participants, biomarker intermediate versus biomarker negative participants, or between two participants that differ by one SD in continuous biomarker levels. Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation; MBI, mild behavioural impairment; Aβ, amyloid β; p-tau, phosphorylated tau; NfL, neurofilament light; GFAP, glial fibrillary acidic protein; APOE e4, apolipoprotein E e4; ADAS-Cog, Alzheimer’s Disease Assessment Scale – Cognitive Subscale.

p-tau217/Aβ42 and p-tau217 positivity were associated with greater cross-sectional odds of MBI (Table 1). Among those with no MBI at baseline, older adults with p-tau217/Aβ42 and p-tau217 positivity exhibited greater hazards for MBI over time (Figure 1).

Figure 1. Survival curves for incident MBI

