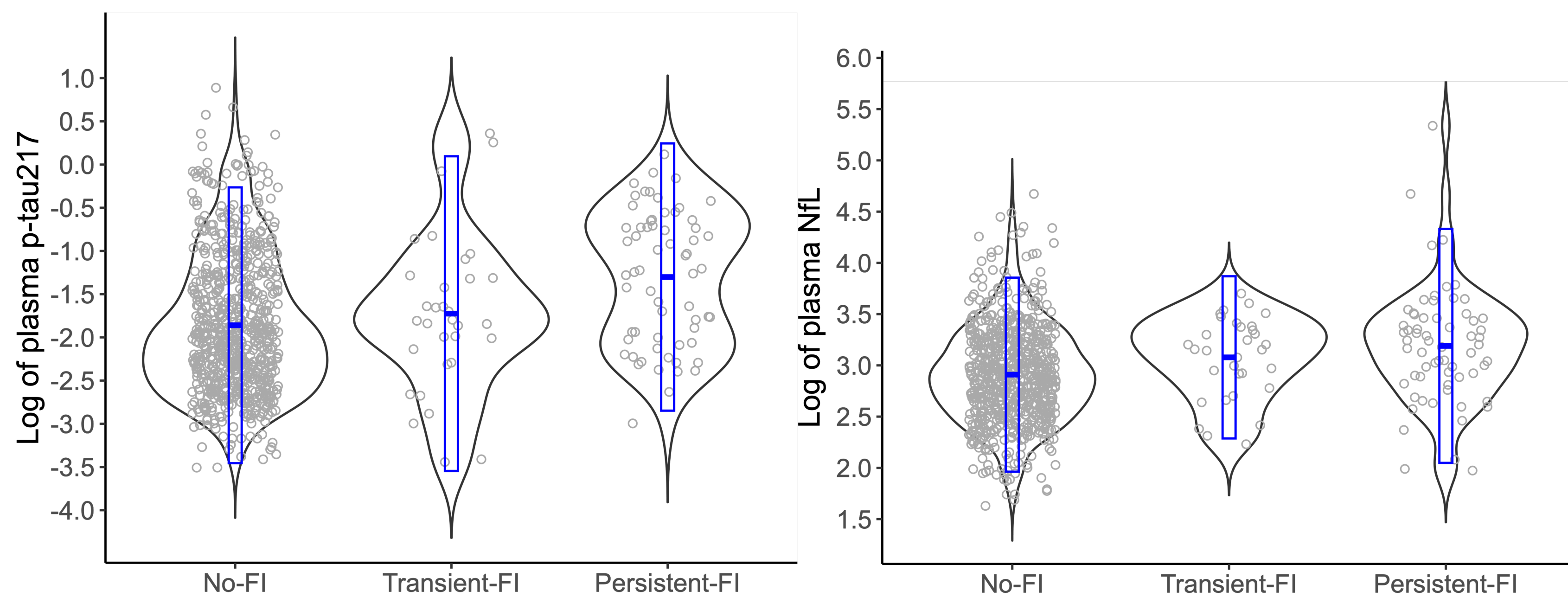


Persistent functional impairment is linked to plasma biomarkers of Alzheimer disease and neurodegeneration, while transient impairment is not.

Persistent functional impairment: Associations with plasma p-tau217 and neurofilament light

Maryam Ghahremani, Zahinoor Ismail

Background	Methods	Results	Conclusions																							
- Functional impairment (FI) refers to the loss of functional independence in performing activities of daily living¹. - FI is a key diagnostic criterion for dementia. - However, subtle but persistent FI may emerge in pre-dementia stages without compromising independence, and signal early neurodegeneration. - Persistent FI refers to functional impairment that is present across multiple visits. - Our recent studies demonstrated that persistent FI is a stronger predictor of cognitive decline and dementia, and related Alzheimer disease (AD) CSF proteinopathies than transient FI^{2,3}. - Building on this evidence, plasma p-tau217 and neurofilament light (NfL) are sensitive biomarkers of AD pathology and neuroaxonal injury; yet their relationship with FI in dementia-free older adults remains unclear.	Sample - Dementia-free participants with normal cognition or mild cognitive impairment from the <i>Alzheimer's Disease Neuroimaging Initiative</i>. Plasma biomarkers - p-tau217 (Lumipulse G1200) - NfL (Simoa Quanterix) Functional ability assessment - Used factor analysis to identify Functional Activities Questionnaire (FAQ)⁴ items that primarily reflect function: - Preparing balanced meals - Preparing warm beverages - Shopping alone - FI score calculated as the sum of scores on the above items. Persistence operationalization - FI present at >2/3 of all pre-dementia study visits, following a validated approach (TTV) to capture mild behavioural impairment⁵. Comparators - Transient FI, not meeting TTV criteria, and no FI. Model: Linear regression Outcome: biomarker levels Covariates: Age, sex, education, MMSE, APOE-ε4 status, neuropsychiatric burden	Sample characteristics: 796 participants with available data. - Age (mean ± standard deviation): 73.6 ± 7.0 % Female: 40.4 % MCI: 34.3 FI groups 701 participants with No-FI 32 participants with Transient-FI 63 participants with Persistent-FI <table><tr><th>Outcome</th><th>Exposure</th><th>exp(β) (%)</th><th>95% CI</th><th>p-value</th></tr><tr><td rowspan="2">p-tau217</td><td>Transient-FI</td><td>0.98</td><td>0.76 - 1.27</td><td>0.894</td></tr><tr><td>Persistent-FI</td><td>1.35</td><td>1.11 - 1.64</td><td>0.003</td></tr><tr><td rowspan="2">NfL</td><td>Transient-FI</td><td>1.07</td><td>0.93 - 1.24</td><td>0.355</td></tr><tr><td>Persistent-FI</td><td>1.18</td><td>1.06 - 1.32</td><td>0.003</td></tr></table>  Persistent FI, compared to transient or no impairment, was associated with significantly greater AD pathology: - Higher plasma p-tau217 - and significantly greater neurodegeneration: - Higher plasma NfL	Outcome	Exposure	exp(β) (%)	95% CI	p-value	p-tau217	Transient-FI	0.98	0.76 - 1.27	0.894	Persistent-FI	1.35	1.11 - 1.64	0.003	NfL	Transient-FI	1.07	0.93 - 1.24	0.355	Persistent-FI	1.18	1.06 - 1.32	0.003	- Persistent, but not transient, functional impairment is associated with higher plasma p-tau217 (AD pathology) and NfL (neurodegeneration). - Operationalizing functional impairment by persistence improves risk stratification, identifying individuals with greater AD pathology and neurodegeneration. - Distinguishing persistent from transient FI enhances the value of FI as an early marker of AD risk. - Like mild behavioural impairment, the natural history of functional impairment matters.
Outcome	Exposure	exp(β) (%)	95% CI	p-value																						
p-tau217	Transient-FI	0.98	0.76 - 1.27	0.894																						
	Persistent-FI	1.35	1.11 - 1.64	0.003																						
NfL	Transient-FI	1.07	0.93 - 1.24	0.355																						
	Persistent-FI	1.18	1.06 - 1.32	0.003																						
Objective			Contact & References																							
Examine cross-sectional associations between plasma p-tau217 and NfL biomarkers and persistent versus transient FI in dementia-free older adults.			