

Longitudinal Associations Of Amyloid-β And Tau With Worry But Not Somatic Anxiety In Cognitively Unimpaired Older Adults

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- I. Higher Aβ and tau burdens are associated with rising anxiety symptoms in cognitively unimpaired older adults, independent of levels of cognitive function and depression.
- II. In cognitively unimpaired older adults, AD pathologies are more specifically associated with rising worry symptoms rather than somatic anxiety symptoms.
- III. Rising late-life worry may be an early neurobehavioral manifestation of AD pathologies prior to cognitive impairment.

INTRODUCTION	METHODS	RESULTS	REFERENCES	
Background: In cognitively unimpaired older (CU) adults, we found that worry—but not other anxiety symptoms—was cross-sectionally associated with higher cortical Aβ (Lee et al., 2024). Here, in a separate neuroimaging cohort, we examined longitudinal reciprocal associations of worry with Aβ and tau to assess worry as a possible neuropsychiatric outcome or <i>possible</i> disease-modifying factor preceding cognitive impairment. Aim 1. To evaluate whether baseline Aβ and tau predict longitudinal change in worry (worry as outcome). Aim 2. To evaluate whether baseline worry predicts longitudinal Aβ and tau accumulation (worry as disease-modifying factor). baseline anxiety → pathology change over time Anxiety GAI: worry, somatic AD pathology Aβ (PiB) · Tau (FTP) baseline pathology → anxiety change over time	- Sample: 140 CU older adults (mean age 77.5±5.9 years; 58%female) from the Harvard Aging Brain Study. - Anxiety measure: Geriatric Anxiety Inventory (GAI) total, worry, and somatic subscale scores. - Aβ/tau: PiB PET DVR (cortical composite) and FTP PET SUVRs in amygdala, entorhinal and inferior temporal cortices were analyzed. - Mixed-effects models adjusted for age, sex, education, depression (GDS), cognition (PACC5) and, in secondary models, effect modification by APOE ε4 status. Total 140 participants Baseline GAI available n = 95 Amyloid PET (PiB) ≥ 2 imaging timepoints n = 96 Tau PET (FTP) ≥ 2 imaging timepoints Separate LMM Outcome: PiB trajectory Predictor: Baseline GAI Separate LMM Outcome: Tau trajectory Predictor: Baseline GAI	- Higher baseline FTP binding predicted increasing total anxiety and worry, but not somatic anxiety. Total β = 0.178, p = 0.020 Worry β = 0.213, p = 0.004 Somatic β = 0.033, p = 0.703 Inferior Temporal Entorhinal Amygdala Total β = 0.119, p = 0.008 Worry β = 0.122, p = 0.005 Somatic β = 0.072, p = 0.151 Total β = 0.142, p = 0.013 Worry β = 0.146, p = 0.008 Somatic β = 0.074, p = 0.245 - Higher baseline PiB binding predicted increasing worry, but not somatic anxiety. Total GAI β = 0.052, p = 0.079 Worry β = 0.067, p = 0.020* Somatic β = -0.008, p = 0.911 Predicted anxiety (z-score) Years from baseline Baseline PiB 1.02 (-1 SD) 1.41 (Mean) 1.81 (+1 SD)	- The Aβ–worry association was primarily driven by APOE ε4 carriers. - Anxiety symptoms did not predict subsequent Aβ or tau accumulation. - Findings remained significant after adjustment for subjective cognitive decline (CFI score). CONCLUSIONS - Higher baseline cortical amyloid and early regional tau were associated with subsequent increases in anxiety symptoms, particularly worry. - Baseline anxiety was not associated with subsequent amyloid or tau accumulation, although this may reflect limited power in the current sample. - Increasing worry may represent an early behavioral indicator of AD pathophysiology in cognitively unimpaired older adults.	Lee S, Zide BS, Palm ST, et al. Specific Association of Worry With Amyloid-β But Not Tau in Cognitively Unimpaired Older Adults. <i>Am J Geriatr Psychiatry</i>. 2024;32(10):1203-1214. doi:10.1016/j.jagp.2024.04.016 CONTACT & FUNDING njdonovan@bwh.harvard.edu This study was supported by the Neuropsychiatry of Aging Research Group (philanthropic funding, NJD), and the Harvard Aging Brain Study is supported by NIA P01AG036694 (RAS, KAJ), AG046396(KAJ). https://habs.mgh.harvard.edu/ ALZHEIMER'S ASSOCIATION AAIC 26