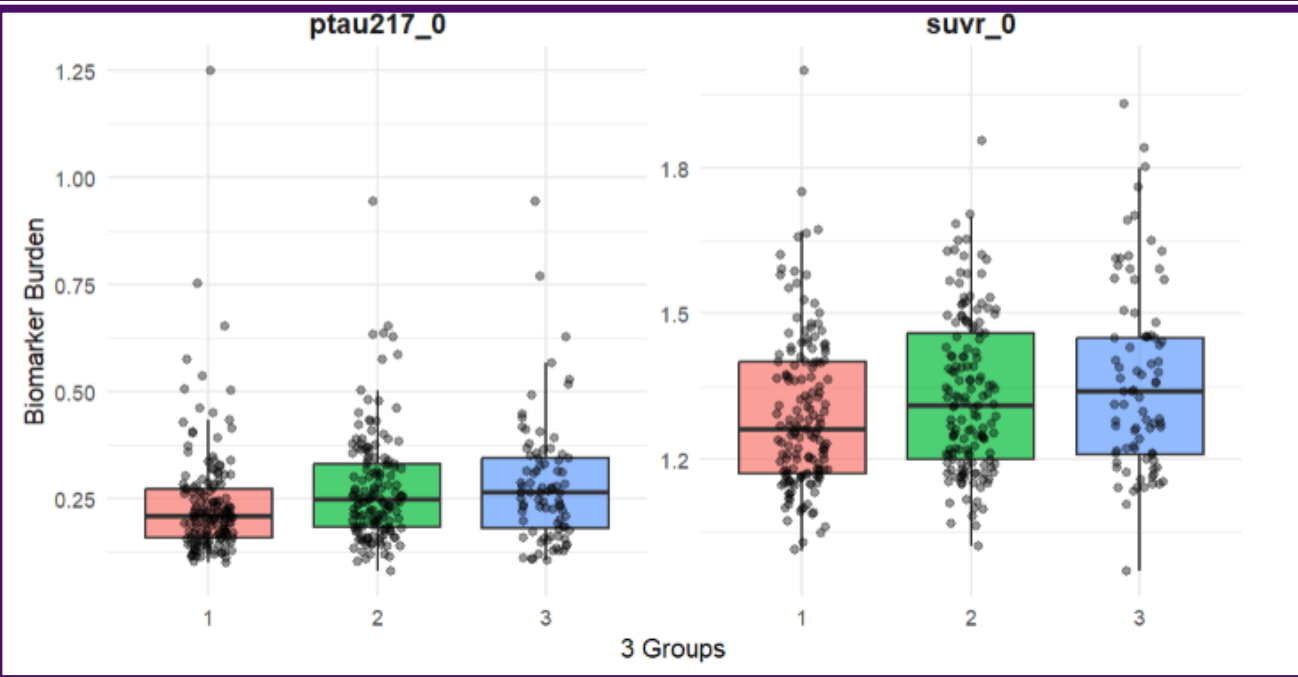


Stratifying Preclinical Alzheimer's Stage 2 criteria predicts biomarker burden among cognitively normal, amyloid positive individuals

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Amyloid positive, cognitively normal individuals who meet multiple Stage 2 criteria may drive group differences between Stage 1 and Stage 2 of preclinical Alzheimer’s disease.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Recent research classifies preclinical AD into two stages:¹ • Stage 1: amyloid positivity with no symptoms • Stage 2: amyloid positivity with transitional cognitive decline (tcd), subjective cognitive decline (scd), or neurobehavioral symptoms (nbs) These staging criteria have predicted decline in prior studies.² It has not yet been addressed how Stage 2 risk might differ based on the number of criteria met, nor how sex differences may impact staging. We hypothesize that individuals who meet multiple criteria exhibit greater risk as a group. Specifically, higher levels of plasma p-tau 217 (p-tau) and brain amyloid (SUVR). We also predict a significant sex effect for p-tau 217.⁴	This analysis included 545 cognitively normal, amyloid positive participants from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study (A4).³ Individuals were categorized into three groups based on number of symptom criteria present. • Group 1 : no tcd, scd, or nbs symptom criteria met (equivalent to Stage 1) Stage 2 was stratified into two groups • Group 2: met criteria for one tcd, scd, or nbs symptom • Group 3: met criteria for multiple staging symptoms Group and sex effects on biomarker burden at baseline were assessed using ANOVA.	 Fig 1. Pairwise comparisons: plasma p-tau 217 and SUVR The main effect of Group on biomarker burden was significant for p-tau ($F = 10.16$, $p = .002$) and SUVR ($F = 20.08$, $p < .001$). There was no significant interaction between group and sex for either biomarker. Females had significantly higher p-tau ($F = 6.45$, $p = .011$). Bonferroni post-hoc analysis revealed higher levels of p-tau in Group 3 compared to Group 1 ($p = .007$). There was no other significant p-tau group difference. Group 3 had higher levels of SUVR compared with Group 1 ($p < .001$) and Group 2 ($p = .041$), which did not differ (from each other (Fig 1).	Group 3 exhibits greater biomarker burden. This provides further support for distinct preclinical Alzheimer’s disease stages defined by tcd, scd, and nbs. These results also suggest that individuals meeting multiple criteria may drive differences between Stage 1 and 2 Future research should assess whether these three-group stratified staging criteria improve prediction of cognitive decline. Future research should also investigate whether stratified staging predicts conversion to clinical cognitive impairment and acceleration of Alzheimer's disease pathology over time.	1. Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Silverberg, N. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. <i>Alzheimer's & dementia</i>, 14(4), 535-562. 2. Kiselica, A. M., & Alzheimer's Disease Neuroimaging Initiative. (2021). Empirically defining the preclinical stages of the Alzheimer's continuum in the Alzheimer's Disease Neuroimaging Initiative. <i>Psychogeriatrics</i>, 21(4), 491-502. 3. Sperling, R. A., Donohue, M. C., Raman, R., Rafii, M. S., Johnson, K., Masters, C. L., ... & Aisen, P. S. (2023). Trial of solanezumab in preclinical Alzheimer's disease. <i>New England Journal of Medicine</i>, 389(12), 1096-1107. 4. Wang, Y. T., Theriault, J., Servaes, S., Tissot, C., Rahmouni, N., Macedo, A. C., ... & Rosa-Neto, P. (2024). Sex-specific modulation of amyloid-β on tau phosphorylation underlies faster tangle accumulation in females. <i>Brain</i>, 147(4), 1497-1510. CONTACT Hannah.Joyce@uga.edu sweet@uga.edu  Department of Psychology Franklin College of Arts and Sciences UNIVERSITY OF GEORGIA  ALZHEIMER'S ASSOCIATION AAIC>26