

Evidence for a Threshold Effect of Amyloid-β on Tau Propagation Beyond the Entorhinal Cortex

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Introduction

Tau spread beyond the entorhinal cortex (EC) drives cognitive decline in Alzheimer's disease, but EC-restricted tau is often clinically silent. The amygdala is anatomically positioned as an important relay beyond the EC into the neocortex, and is also linked to neuropsychiatric symptoms of dementia, making it a candidate marker of clinically meaningful disease transition.¹

Amyloid-β (Aβ) is thought to permit this spread: recent ADNI/HABS data showed a nonlinear, Aβ-dependent acceleration of tau spread from the EC, peaking at intermediate Aβ levels.² Whether a specific Aβ threshold gates tau entry into the amygdala, and whether this transition marks the onset of cognitive impairment, remains untested.

Methods

875 AIBL participants (cognitively unimpaired, MCI, or AD) with ¹⁸F-MK6240 tau PET and Aβ PET (Centiloid, CL) were classified by regional tau pattern: Negative, Entorhinal-restricted, Entorhinal + Amygdalar, or Neocortical, using cerebellum-referenced SUVR thresholds (2 SD above tau-negative, CL<15 controls). Entorhinal + amygdalar involvement produced a characteristic curved "hook sign" on sagittal PET (Figure 1).³

Cross-sectional associations between Aβ, tau subgroup, and diagnosis were modelled with ordinal/binary logistic regression. In 274 participants with serial tau PET, linear mixed-effects models assessed cognitive trajectories (sMMSE, CDR-SoB) by tau subgroup. In 189 participants with baseline Negative/Entorhinal-restricted tau, Cox proportional hazards modelled Aβ-driven tau progression; Kaplan-Meier analysis tested clinical progression based on Aβ thresholds.

Clinical Impairment and Aβ Burden Across Tau Subgroups

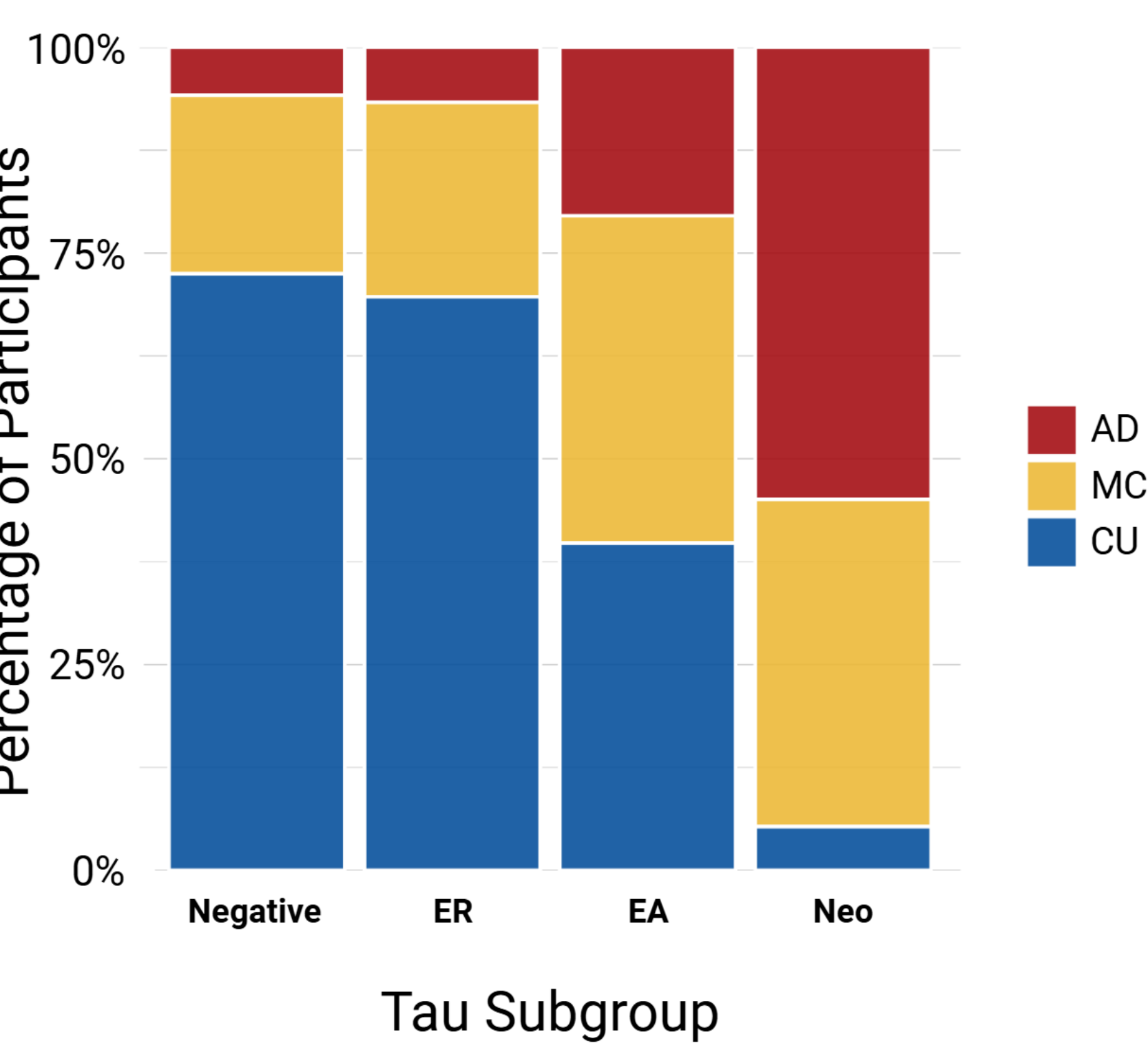


Figure 4 | Distribution of Clinical Diagnosis at First Tau PET Scan. Proportion of participants with a diagnosis of cognitively unimpaired (CU, blue), mild cognitive impairment due to Alzheimer's disease (MCI, yellow), and Alzheimer's dementia (AD, red), for each tau subgroup at the time of first tau PET scan.

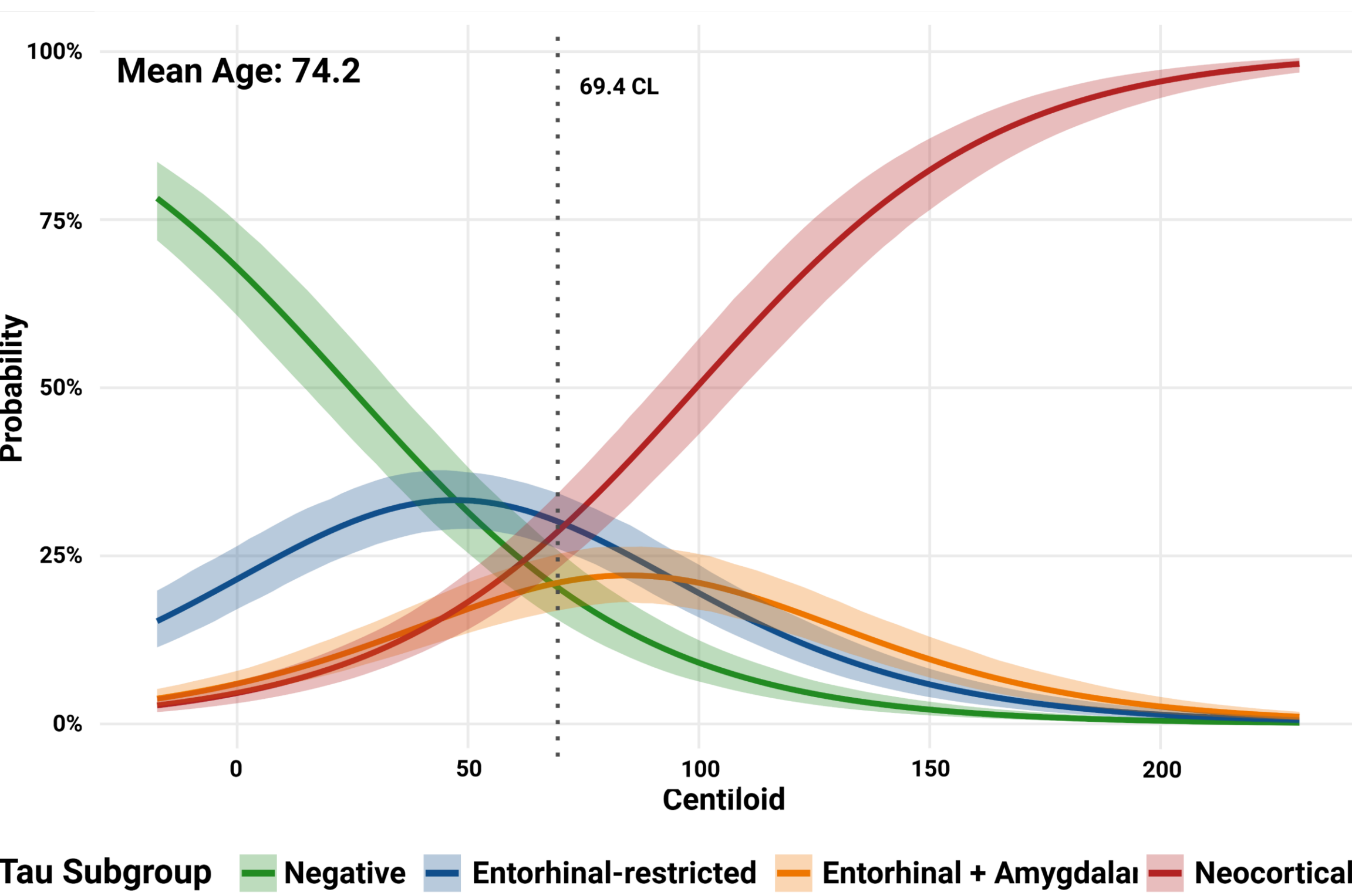


Figure 5 | Predicted Probabilities of Tau Spread by Amyloid-β burden. Probability curves predicting tau subgroups based on Centiloid values, adjusted for mean age at Aβ PET scan (74.2), gender (female), APOE E4 status (carrier). Shaded ribbons indicate 95% confidence intervals. Dashed line indicates the Centiloid threshold (69.4 CL, 95% CI: 59.6–78.7 CL) at which amygdalar or neocortical tau deposition became the more probable outcome.

Demographics

Table 1 Cross-sectional characteristics across tau subgroups.				
Tau subgroups at first ¹⁸ F-MK6240 tau PET	Negative N = 378	Entorhinal-Restricted N = 165	Entorhinal + Amygdalar N = 88	Neocortical N = 244
Age*	74.0 (69.7 - 78.0)	75.9 (72.0 - 81.2)	76.4 (72.3 - 81.5)	72.7 (67.7 - 77.8)
Gender (Female)	175 (46%)	86 (52%)	47 (53%)	121 (50%)
Years of Education	12 (11 - 16)	12 (11 - 16)	12 (10 - 15)	12 (10 - 15)
APOE4 Carrier*	117 (31%)	59 (36%)	60 (68%)	162 (66%)
Diagnosis*				
Cognitively Unimpaired	274 (72%)	115 (70%)	35 (40%)	13 (5%)
Mild Cognitive Impairment	82 (22%)	39 (23%)	35 (40%)	97 (40%)
Dementia*	22 (6%)	11 (7%)	18 (20%)	134 (55%)
sMMSE*	29.0 (27.0 - 29.0)	28.0 (27.0 - 29.0)	27.0 (25.0 - 29.0)	24.0 (22.0 - 27.0)
CDR Sum of Boxes*	0.0 (0.0 - 0.5)	0.0 (0.0 - 0.5)	0.5 (0.0 - 2.5)	3.0 (1.5 - 4.5)
Centiloid*	4.3 (-3.1 - 27.9)	10.9 (-1.3 - 57.6)	102.1 (63.6 - 127.1)	121.0 (97.2 - 143.6)
Above 25CL*	106 (28%)	66 (40%)	81 (93%)	240 (99%)
Above 50CL*	60 (16%)	47 (28%)	70 (80%)	233 (96%)

n (%); Median (Q1 - Q3).
*adjusted P < 0.005 (Pearson's Chi-squared for APOE4 Carrier, Diagnosis, Above 25CL, Above 50CL;
Kruskal-Wallis rank sum for Age, Centiloid, MMSE, CDR Global Score, CDR Sum of Boxes).
*due to Alzheimer's disease.

18F-MK6240 Tau PET Segmentation

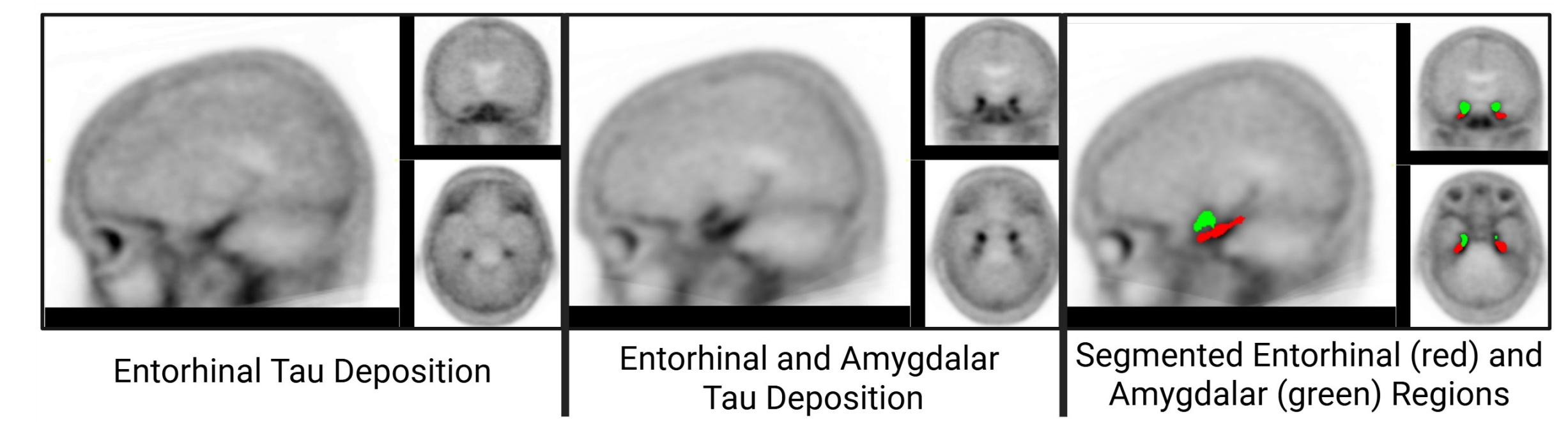


Figure 1 | Tau PET Segmentation. Segmented Tau PET images demonstrating tracer uptake in the entorhinal cortex (red) and the amygdala (green). Regional quantification determined tau subgroups: Negative, Entorhinal-Restricted (ER), Entorhinal + Amygdalar (EA), and Neocortical (Neo).

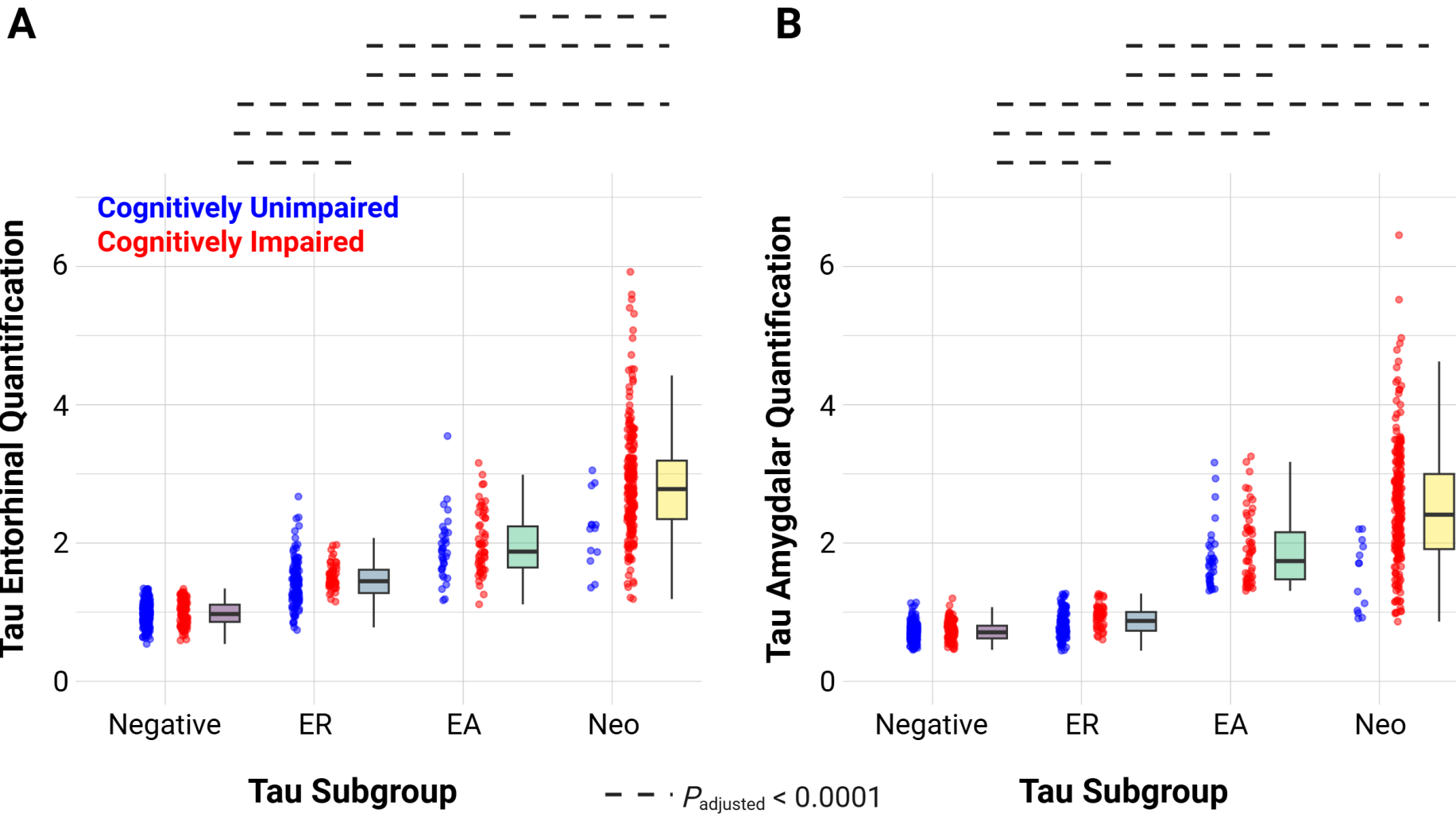


Figure 2 | Regional Tau PET Quantification. Distribution of 18F-MK6240 tau SUVR in Entorhinal Cortex (A) and Amygdala (B) for each tau subgroup of cognitively unimpaired (blue) and impaired (red) participants. Dashed line - $p_{adjusted} < 0.0001$, solid line - $p_{adjusted} < 0.05$ between deposition groups (all participants regardless of cognitive status).

Aβ by Tau Subgroup

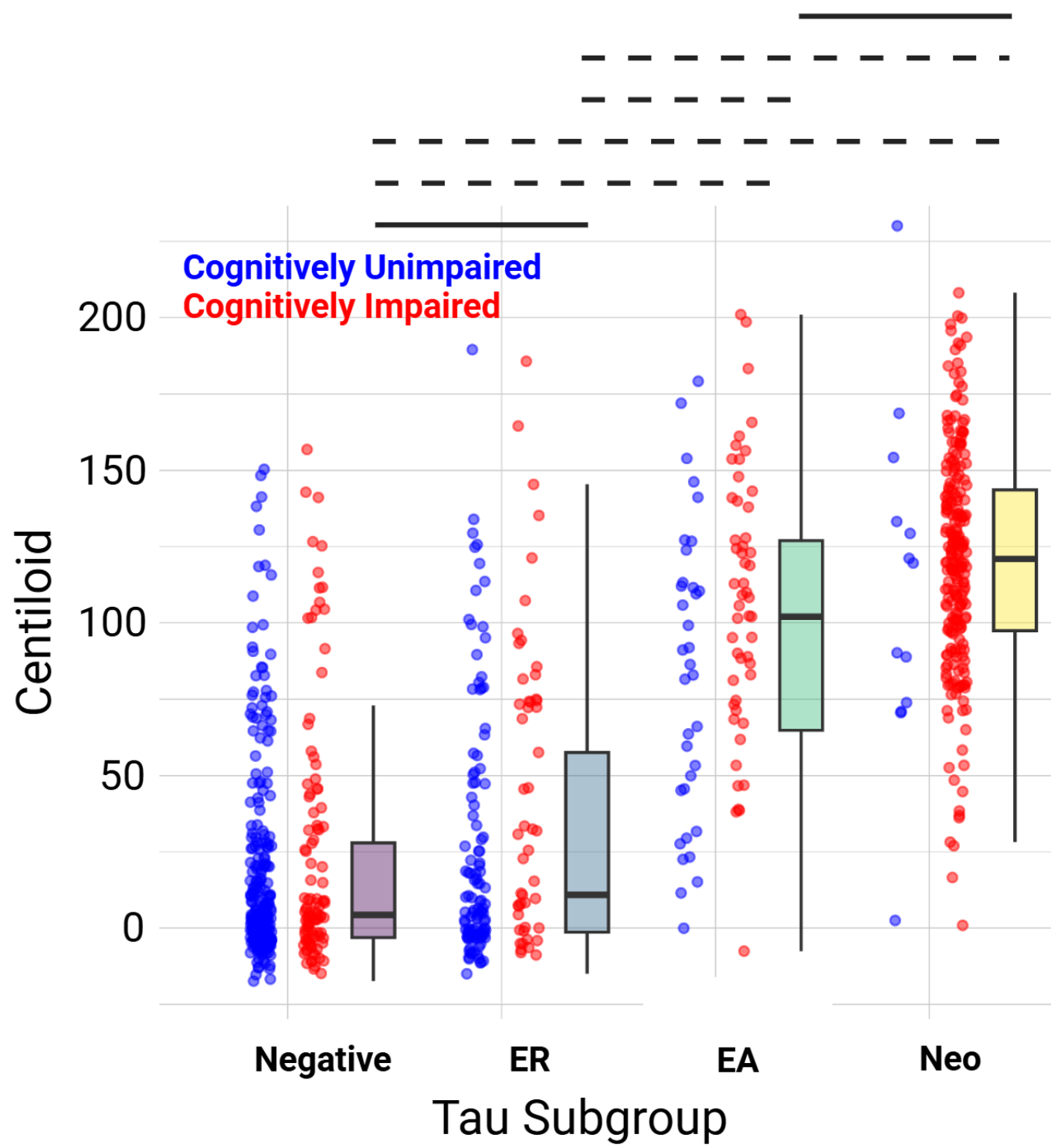


Figure 3 | Distribution of CL by Tau Subgroup. Distribution of each tau subgroup for cognitively unimpaired (blue) and impaired (red) participants. Dashed line - $p_{adjusted} < 0.0001$, solid line - $p_{adjusted} < 0.05$ between deposition groups (all participants regardless of cognitive status).

Clinical Progression at 70CL

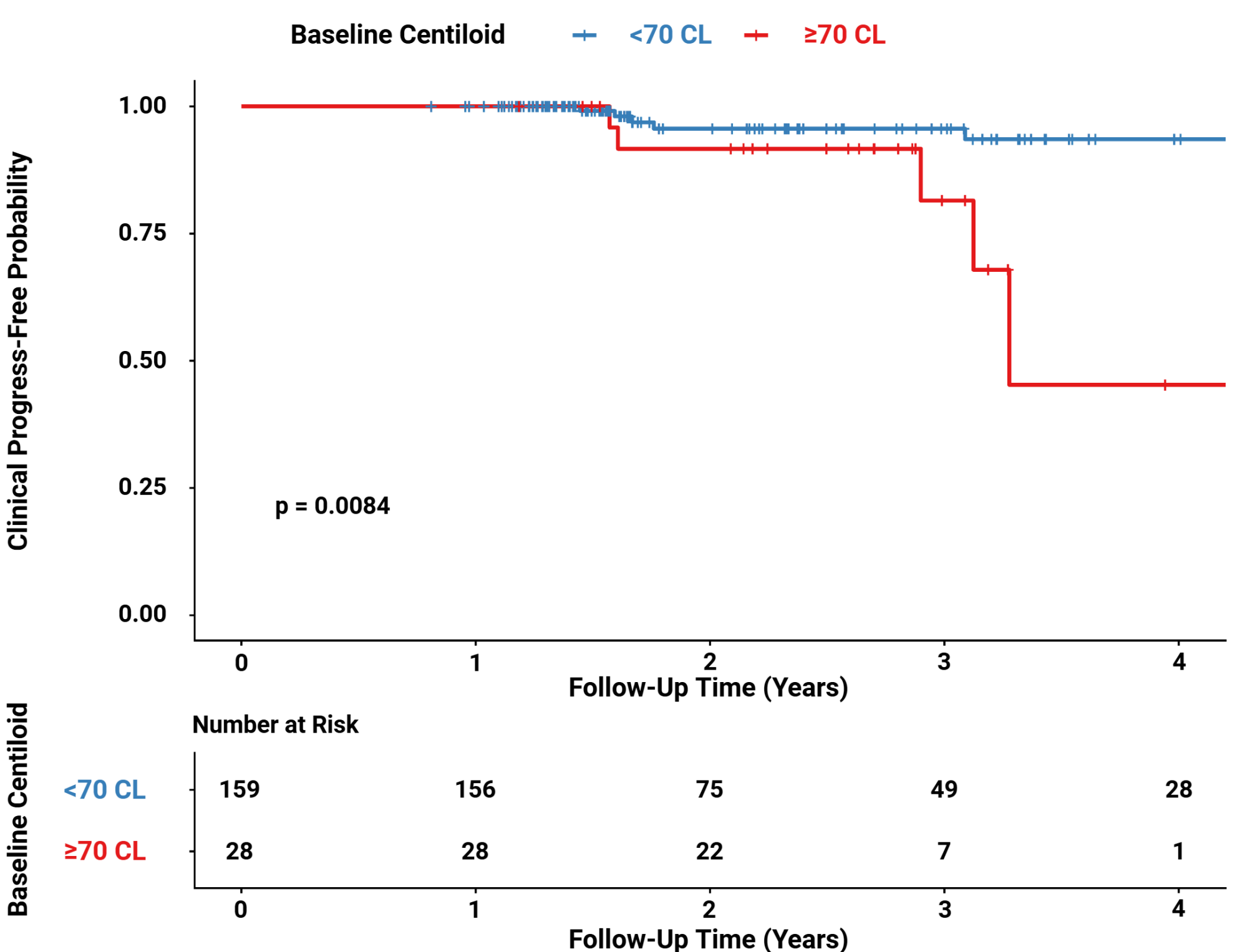


Figure 6 | Kaplan-Meier Estimates of Clinical Progression by Baseline Amyloid-β Burden. Survival curves for the baseline clinical state (cognitively unimpaired or mild cognitive impairment). Participants stratified by baseline Aβ PET levels using a 70 CL threshold. ≥ 70 CL was associated with a significantly higher risk of clinical progression (Log-rank $p = 0.0084$).

Conclusion

Amygdalar tau spread, gated by an Aβ threshold of ~60–80 CL, marks a key biological and clinical inflection point in Alzheimer's disease. Tau confined to the entorhinal cortex is largely clinically silent, but becomes consequential once Aβ burden permits spread into the amygdala, where risk of cognitive impairment rises sharply.

This 60–80 CL window converges with prior ADNI/HABS findings, cross-validating the threshold across cohorts and tau tracers. Our findings also highlight the potential importance of amygdalar tau on clinical progression.

These findings support early intervention before this threshold is reached, and offer a refined framework for patient stratification and trial design.

Acknowledgements

We thank the AIBL study participants and their families for their invaluable and ongoing contribution to dementia research, and the AIBL study team for data collection and management.

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