

The 60-Centiloid Threshold: A Critical Tipping Point For Tau Pathology And Cognitive Decline In Alzheimer’s Disease

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- **Plasma p-tau217 rises early during low amyloid accumulation across all assay platforms and cohorts.**
- **Tau PET shows a downstream inflection near CL 60, becoming significant at the 40–59 → 60–79 transition.**
- **Cognitive decline becomes most prominent at high amyloid burden.**

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INTRODUCTION

- Amyloid-β (Aβ) positivity, conventionally defined at approximately CL 20, encompasses a wide range of Aβ burden and considerable clinical heterogeneity. Many "low-positive" individuals do not show accelerated decline, suggesting that the biological consequences of Aβ may emerge only above a higher burden.
- We hypothesized that a downstream "tipping point"—where tau pathology and clinical decline accelerate—occurs at a higher Aβ level than the positivity threshold.
- Using two independent cohorts and multiple biomarker platforms, we examined how plasma p-tau217, tau PET, and longitudinal cognition change across the Centiloid (CL) continuum, and whether CL 60 represents a critical transition.

METHODS

- **Participants.** Early-stage AD (MCI or DAT; CDR 0.5–1.0) from the K-ROAD and ADNI cohorts, analyzed in two subdatasets: a plasma biomarker subdataset (K-ROAD n = 1,243; ADNI n = 551) and a tau PET subdataset (K-ROAD n = 156; ADNI n = 467).
- **Measures**
 - Plasma p-tau217 was measured across platforms (K-ROAD: Simoa/ALZpath, Roche; ADNI: ALZpath, Fujirebio, Janssen).
 - Tau PET was quantified as temporal meta ROI SUVR.
 - Aβ burden was expressed on the Centiloid scale and grouped into consecutive intervals: CL 0–24, 25–39, 40–59, 60–79, and ≥80.
- **Analysis.** Planned comparisons tested differences in each biomarker between adjacent CL groups, adjusting for age, sex, and APOE ε4 status. Longitudinal CDR-SOB trajectories were modeled with linear mixed-effects models adjusted for age, sex, APOE ε4, and diagnosis.

RESULTS

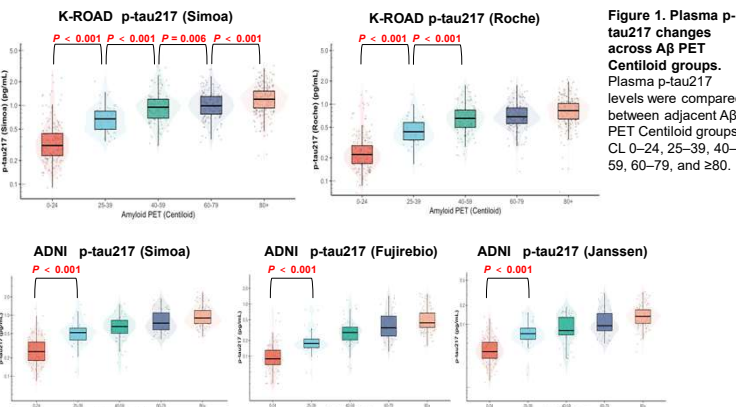
Table. Demographic characteristics by cohort and biomarker subdataset

Characteristic	K-ROAD	ADNI	P value
Plasma biomarker subdataset			
Participants, n	1243	551	
Age, mean (SD), years	71.2 (8.7)	74.7 (8.5)	<0.001
Female, n (%)	764 (61.5)	252 (45.7)	<0.001
Education, mean (SD), years	11.3 (4.7)	16.0 (2.7)	<0.001
APOE ε4 carrier, n/N (%)	601/1239 (48.5)	262/527 (49.7)	0.680
Diagnosis, n (%)			<0.001
MCI	766 (61.6)	399 (72.4)	
DAT	477 (38.4)	152 (27.6)	
Aβ PET Centiloid, mean (SD)	55.5 (45.0)	52.3 (52.2)	0.210
Tau PET subdataset			
Participants, n	156	467	
Age, mean (SD), years	71.5 (9.2)	74.5 (8.5)	<0.001
Female, n (%)	98 (62.8)	219 (46.9)	<0.001
Education, mean (SD), years	11.8 (4.4)	16.0 (2.6)	<0.001
APOE ε4 carrier, n/N (%)	85/153 (55.6)	215/449 (47.9)	0.122
Diagnosis, n (%)			<0.001
MCI	64 (41.0)	362 (77.5)	
DAT	92 (59.0)	105 (22.5)	
Aβ PET Centiloid, mean (SD)	76.2 (38.4)	50.7 (51.9)	<0.001
Tau PET SUVR (Temporal meta ROI), mean (SD)	1.83 (0.57)	1.42 (0.44)	<0.001

Values are mean (SD) or n/N (%) where applicable. P values compare K-ROAD and ADNI within each subdataset and are descriptive.

Plasma p-tau217 rises early

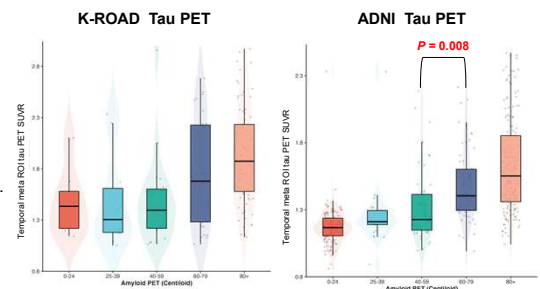
- Across all platforms, plasma p-tau217 increased at the earliest transition, indicating sensitivity to low Aβ burden.
- In K-ROAD, stepwise increases continued through CL 40–59, whereas in ADNI the change was concentrated at the earliest interval.



Tau PET inflects near CL 60

- Tau PET SUVR did not increase significantly at lower intervals but rose at the 40–59 → 60–79 transition in ADNI (P = 0.008), supporting a downstream inflection around CL 60.
- K-ROAD showed the same directional trend without reaching significance, consistent with a smaller tau PET sample.

Figure 2. Tau PET signal shows a downstream inflection around CL60
Tau PET SUVR in the temporal meta ROI was compared across adjacent Aβ PET Centiloid groups.



Clinical decline accelerates with higher burden

- Longitudinal CDR-SOB trajectories worsened progressively across increasing CL groups.
- Decline followed a graded pattern that became clinically pronounced at CL ≥ 60, with the highest-burden groups (60–79, ≥80) declining fastest (K-ROAD P = 0.002; ADNI P = 0.038).

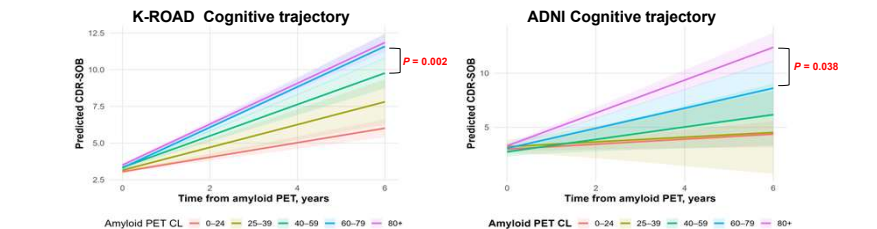


Figure 3. Longitudinal cognitive and functional trajectories by Aβ PET Centiloid group
Predicted longitudinal trajectories were estimated using linear mixed-effects models adjusted for age, sex, APOE ε4 status, and diagnosis. Higher Aβ burden was associated with faster clinical worsening.

* Although statistical clarity differed by cohort and modality, the direction of findings was concordant across cohorts. These differences likely reflect subdataset-specific sample size, Aβ burden distribution, and diagnostic composition.

CONCLUSIONS

- Plasma p-tau217 detects amyloid-related change early, whereas tau PET inflects near CL60, most clearly in the ADNI temporal meta ROI, identifying CL60 as a biologically meaningful tipping point for downstream tau pathology.
- Longitudinal CDR-SOB trajectories showed faster clinical-functional worsening with higher Aβ burden (≈CL 60 in K-ROAD, ≈CL 80 in ADNI).
- These findings support the use of quantitative Aβ burden—not Aβ positivity alone—for prognosis, patient selection for disease-modifying therapy, and clinical trial design.