

Introduction

- Neurodegeneration encompasses progressive loss of neuronal structure or function, including brain atrophy, axonal injury, and synaptic degeneration¹.
- Moreover, synaptic and structural neurodegeneration are temporally and biologically dissociated in Alzheimer's disease (AD)².
- Yet, current AD biomarker frameworks capture neurodegeneration by measuring hippocampal atrophy (HCV), axonal injury, and glucose uptake, but not synaptic degeneration³.
- Aim: to test whether separating synaptic and structural neurodegeneration identifies clinically meaningful heterogeneity and improves risk stratification across the AD continuum.**

Methods

- Participants:** 1,217 individuals from ADNI, a well-characterized cohort spanning the AD continuum: mean age $\pm$ SD 73 $\pm$ 7.2 years; 47% female; 36% cognitively unimpaired (CU) 46% mild cognitive impairment (MCI), 18% AD dementia; APOE ϵ 4 carriage 48%; A β -positive 62%. Additionally, we included 139 individuals across the AD continuum, from TRIAD for validation (McGill, Canada; data not shown)
- S/N classification:** Individuals were classified by synaptic degeneration (S) indexed by CSF GAP43, SNAP25, neurogranin, and total-tau (t-tau)^{4,5}, and by structural neurodegeneration (N) indexed by HCV³, based on published cutoffs^{4,6}.
- We compared biomarker profiles and progression risk.

Results

Demographics: **a)** Participants spanned all four S/N groups: S-N- (45%, n=549), S+N- (26%, n=323), S-N+ (11%, n=129), and S+N+ (18%, n=216), which were stable over 10 years (reversal <1%). **b)** S+N+ was rare in CU A β -negative individuals (1%, 3/268) but rose to 33% (190/577) in cognitively impaired A β -positive individuals, while S-N- declined from 73% (196/268) to 22% (127/577) across the same groups.

Transitions in S/N groups

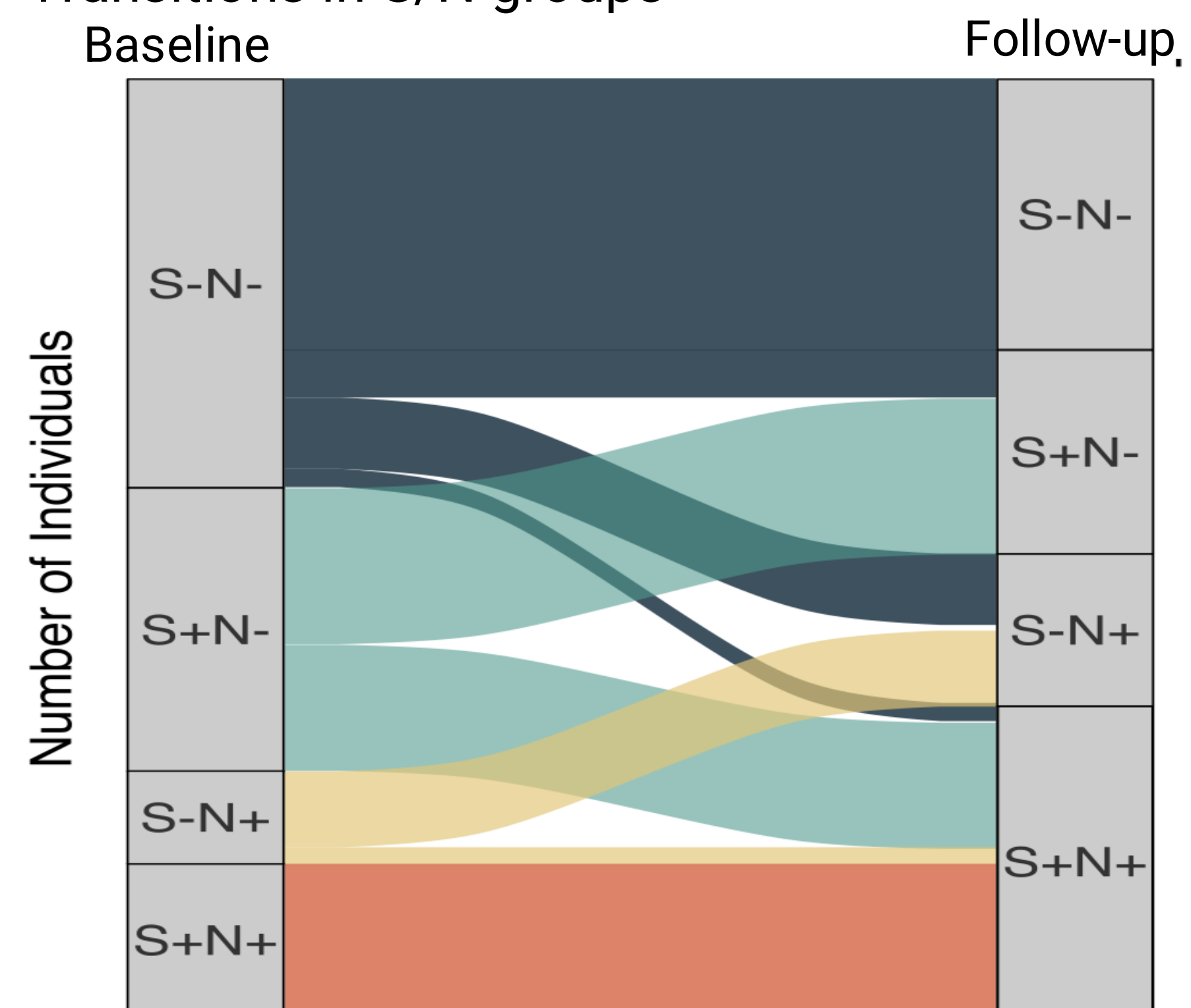


Figure 1. Isolated synaptic degeneration is the profile most likely to transition to dual pathology. Sankey diagram shows changes between S/N groups from baseline to last follow-up (median [IQR] follow-up =3.97 [2.03–6.04] years). S+N- showed the highest conversion rate: 45% developed structural neurodegeneration versus 19% of S-N+ who developed synaptic degeneration. Cox proportional hazard models adjusted for age, sex, cognitive status revealed that isolated synaptic degeneration halved time to structural neurodegeneration onset (2.02 vs 4.02 years; $p < 0.0001$), whereas the reverse was not observed ($p = 0.20$).

Probability of pathological and cognitive outcomes

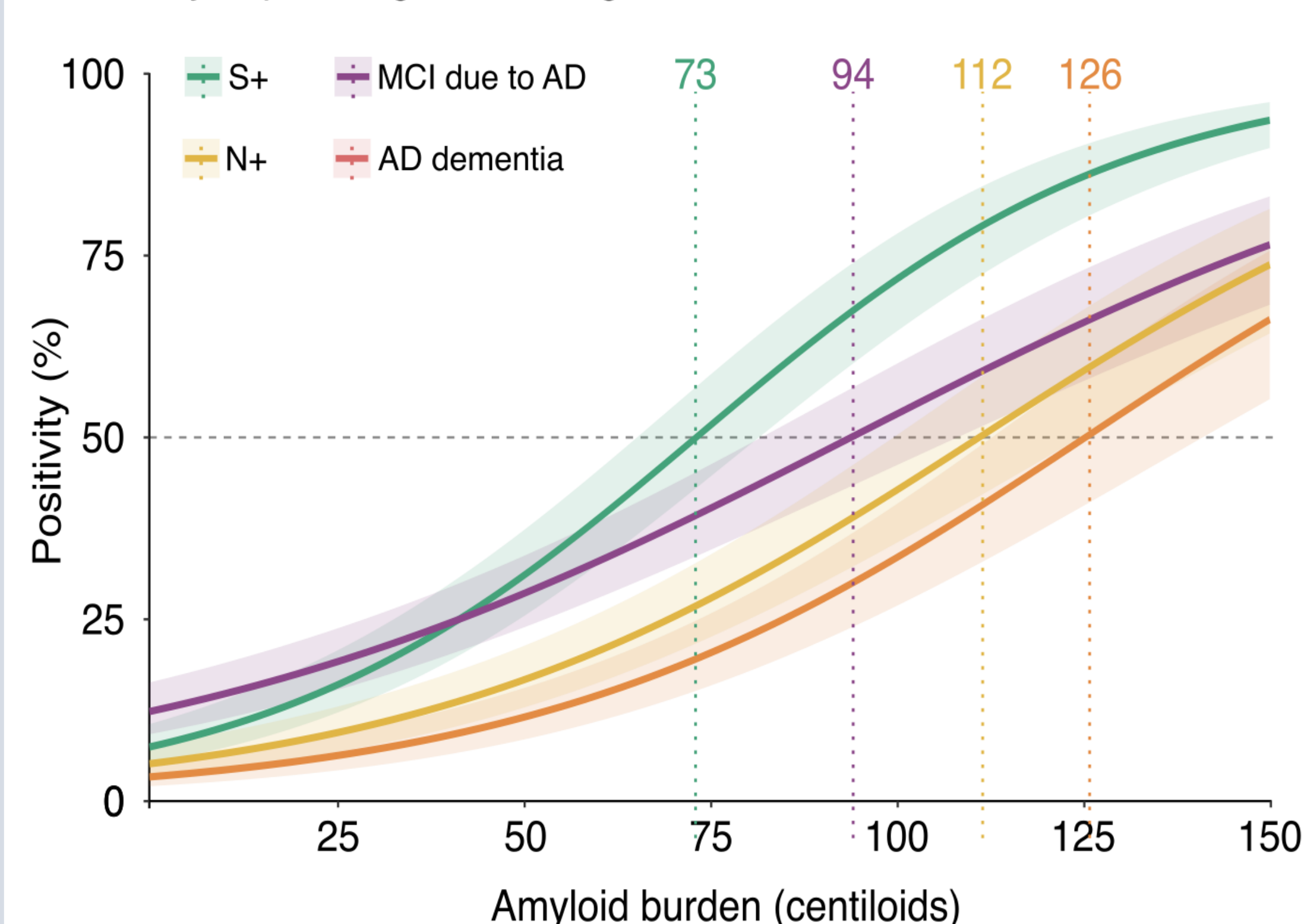


Figure 2. Synaptic degeneration emerges before MCI onset, whereas structural neurodegeneration emerges later. Probability of S+, N+, MCI due to AD, and AD dementia as a function of A β burden (centiloid 'CL' scale) from logistic regression models (n = 821 with available A β -PET). Synaptic degeneration reached 50% positivity at 73 CL, before MCI onset (94 CL), whereas structural neurodegeneration followed at 112 CL. Shaded regions indicate 95% confidence intervals.

Summary

- First large-scale AD longitudinal study to operationalize synaptic and structural neurodegeneration as independent dimensions, identifying four clinically distinct profiles.
- S+N- is the profile most likely to transition to dual pathology (45% vs 19% of S-N+).
- Synaptic degeneration emerges before MCI onset (73 CL); structural neurodegeneration follows (112 CL).
- Isolated synaptic degeneration elevated four-year risk of cognitive decline (26.4% vs 8.9%; HR 3.44).
- Synaptic degeneration added prognostic value beyond A β and structural neurodegeneration.

Cognitive decline across S/N groups at baseline

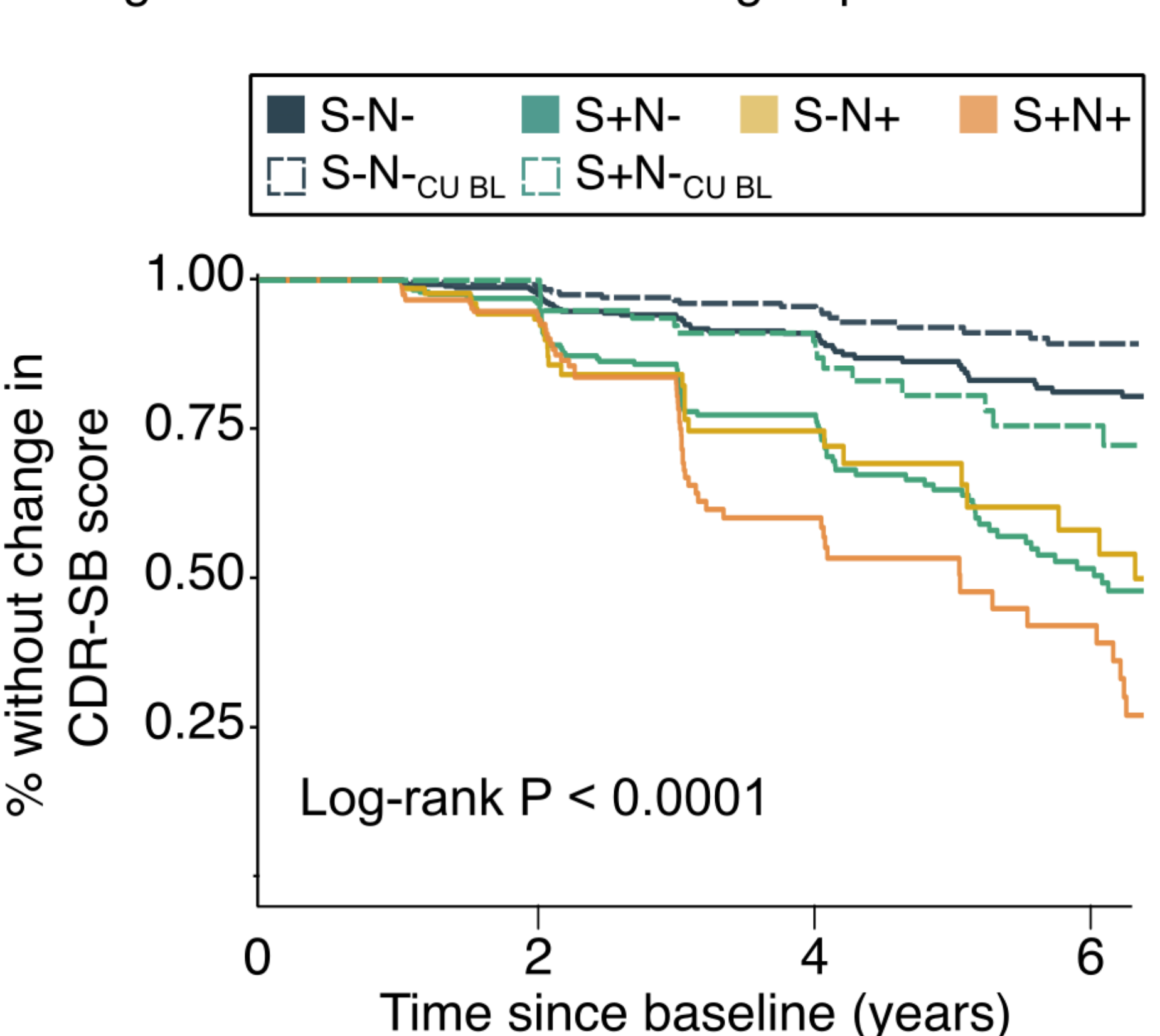


Figure 3. Isolated synaptic degeneration markedly increases the risk of cognitive decline. Kaplan-Meier curves derived from Cox proportional hazards models show time to Clinical Dementia Rating sum-of-boxes (CDR-SB) increase across S/N groups in all participants at baseline and in CU individuals only (S-N- and S+N- CU BL). Isolated synaptic degeneration conferred a four-year absolute risk of 26.4% versus 8.9% in S-N- (HR 3.44, 95% CI 2.51-4.71), including in CU individuals (HR 3.04, 95% CI 1.76-5.24; four-year absolute risk 14.3%). Dual pathology conferred the highest risk (HR 4.78; absolute risk 48.7%). Models were adjusted for age, sex, education, and baseline CDR-SB.

Table 1 | Synaptic degeneration adds risk beyond A β and structural neurodegeneration

Outcome	Estimate (95% CI)	P value
Rate of CDR-SB decline		
S+ $\times$ time interaction (beyond A β + N)	+0.40 pts/yr (0.17-0.63)	<0.001
Progression risk S+ vs S-	OR 1.73 (1.07-2.85)	0.026
Group-specific CDR-SB decline rates		
S-N- (reference)	0.34 pts/yr (0.14-0.52)	-
S+N- isolated synaptic degeneration	0.65 pts/yr (0.48-0.82)	-
S+N+ dual pathology	1.47 pts/yr (1.23-1.72)	-
S $\times$ N synergy		
Beyond independent effects	$\chi^2(2) = 6.28$	0.043

To test whether synaptic degeneration carries prognostic information beyond A β and structural neurodegeneration, we compared linear mixed-effects and logistic regression models with and without synaptic degeneration in 422 A β -positive individuals, measuring cognitive decline using the CDR-SB, adjusted for A β burden, age, sex, education, and baseline CDR-SB. Synaptic degeneration improved model fit, independently accelerating decline by 0.40 points/year and increasing progression odds by 73%. To test whether combined pathology causes more harm than each alone, we extended the linear mixed-effects model with an S $\times$ N $\times$ time interaction: dual pathology (S+N+) declined nearly four times faster than neither (1.47 vs 0.34 points/year), with synergy beyond their combined effects.

Conclusion

Separating synaptic from structural neurodegeneration across the AD continuum reveals S+N- as an early stage preceding structural injury, with independent prognostic value for clinical decline. Our findings refine biomarker frameworks and enables prognostic enrichment for prevention trials.

References

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Acknowledgments



Contact

soaresk@pitt.edu

