

Supplement

Supplemental results and discussion

CSF p181 mirrors plasma p181 in A+SCD vs A-SCD, but not in A+CU vs A+SCD

The cross-sectional biomarker findings for CSF p181 were similar to those for plasma p181 (Fig. S1C); however, CSF p181 could not distinguish between the A+CU and A+SCD groups. Conversely, it showed an increase in the A+MCI group compared to the A+SCD group, where plasma p181 levels had already flattened out. This suggests that plasma p181 may be more sensitive in detecting p-tau pathology in A+SCD. However, further studies are needed to replicate these results.

Baseline levels of plasma p181 are associated with hippocampal volume loss in A+MCI, but not in A+SCD

Hippocampal volumes at baseline were lower in SCD compared CU (3061 ± 21 vs 3148 ± 28 mm³, $p=0.016$), and even further reduced in MCI individuals (2885 ± 36 mm³, $p<0.001$, Fig. S2). Within A+MCI, but not yet in the A+SCD, baseline ptau181 levels showed a qualitative association with lower hippocampal volume (A+MCI: $p=0.119$, A+SCD: $p=0.439$). Baseline NfL levels were not associated with lower hippocampal volume in any of the pre-dementia stages (Fig. S3).

Supplemental figure captions

Supplemental Figure 1. The CSF A β 42/40 ratio separates A+ from A- clinical groups, and CSF p181 replicates findings in plasma p181 in A+SCD vs A-SCD, but not between A+CU vs A+SCD.

Baseline CSF of CU (blue), SCD (red), MCI (green), and AD (purple) of the same patients as in Figure 1A was analyzed using ELISAs to measure **(A)** the A β 42/40 ratio **(B)** mid-region tau

(=total tau) and **(C)** p181. In both graphs, each point represents an individual subject, and means \pm SEM are indicated. Differences between groups were assessed using Welch-ANOVA followed by Dunnetts post hoc test for the contrasts indicated, * $p < 0.05$, ** $p < 0.01$, *** $p < .001$, **** $p < 0.0001$, ns, non-significant. **(A)** The CSF A β 42/40 ratio, **(B)** CSF mid-region tau, and **(C)** CSF p181 separates A-SCD from A+SCD and is increased in A+MCI compared to A+SCD, but not in A+SCD vs A+CU.

Supplemental Figure 2. Plasma NfL levels are not associated with future cognitive decline in A+SCD. (C) Baseline plasma NfL levels predict future cognitive decline only in the MCI stage, lacking notable relevance in both A+CU **(A)** and A+SCD **(B)**. Trajectories are modeled as outlined in Figure 3, incorporating an interaction term of time and baseline NfL levels.

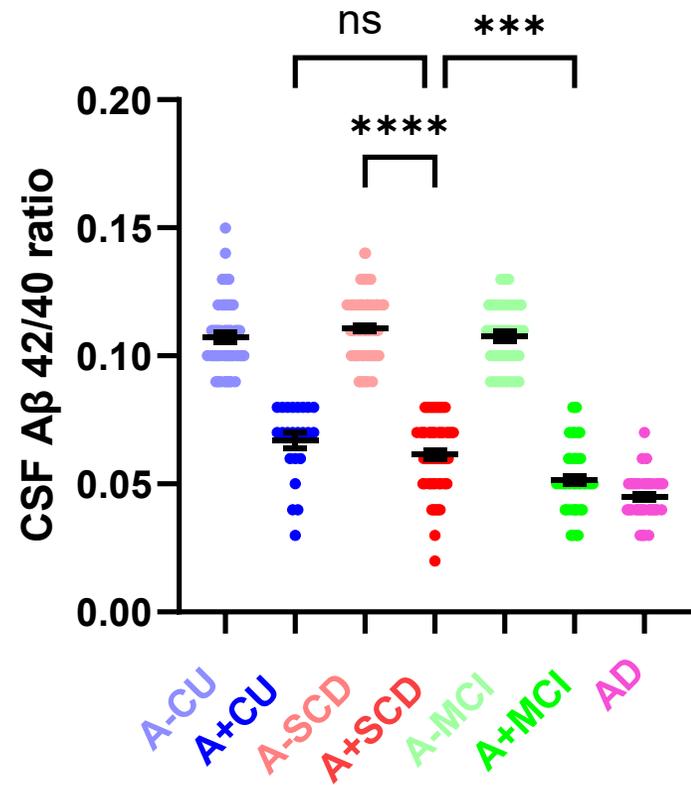
Supplemental Figure 3. Hippocampal volume loss in A+MCI is associated with higher baseline levels of plasma p181. Longitudinal trajectories of whole hippocampal volumes of **(A)** CU (blue), **(B)** SCD (red), and **(C)** MCI (green) individuals, stratified by CSF amyloid-positivity are depicted. Dashed black lines indicate the trajectories for the clinical groups irrespective of the CSF amyloid status. Reduced hippocampal volumes are noted in SCD compared to CU individuals. Subsequently, hippocampal volumes experience further reduction in the MCI stage, reaching their lowest levels in A+MCI. In panel **(D – F)**, baseline (BL) plasma p181 levels of the A+CU, A+SCD, and A+MCI group, categorized into a low (light grey), mid (medium grey), and high (dark grey) tertile, were used to predict whole hippocampal volumes at baseline and longitudinally over the study period of four years. In the A+MCI group, higher baseline ptau181 levels are qualitatively associated with reduced hippocampal volume. Trajectories are derived from linear mixed models with an interaction term for time and baseline p181 levels, and adjusted for age at baseline, sex, and total brain volume.

Supplemental Figure 4. Hippocampal volume loss is not correlated with baseline NfL. (A - C) Higher NfL levels at baseline are not associated with lower hippocampal volume in pre-dementia AD stages. Trajectories are modeled as outlined in Supplemental Figure 3, but with an interaction term of time and tertiles of baseline NfL levels.

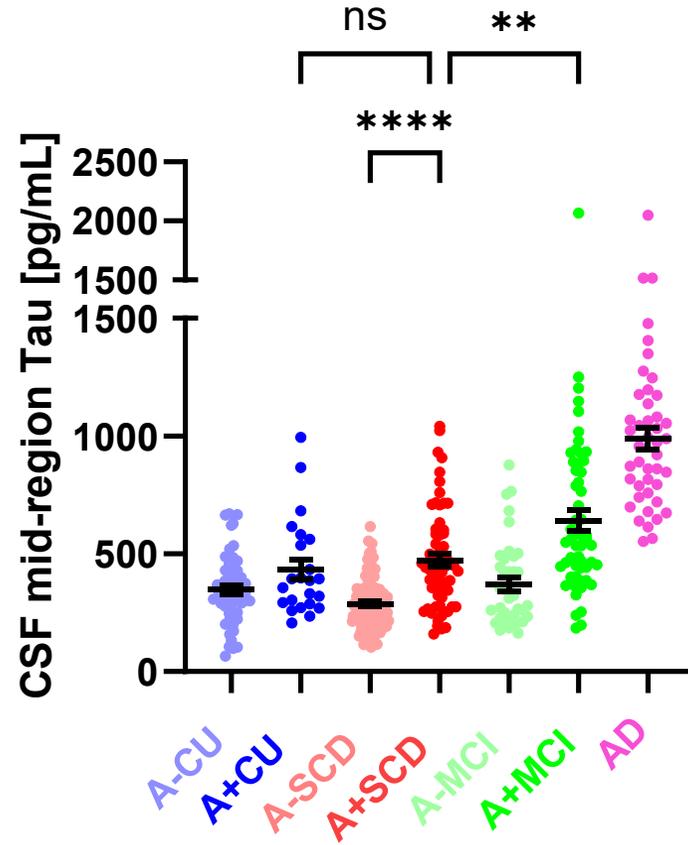
Supplemental Figure 5. Higher NfL levels at baseline do not predict clinical stage transition in A+SCD and A+MCI. Survival curves for **(A)** A+SCD and **(B)** A+MCI indicate, that higher NfL levels do not predict future progression to **(A)** MCI or **(B)** dementia. Statistical interference and labeling of the graphs are as outlined in Figure 4.

SFigure 1

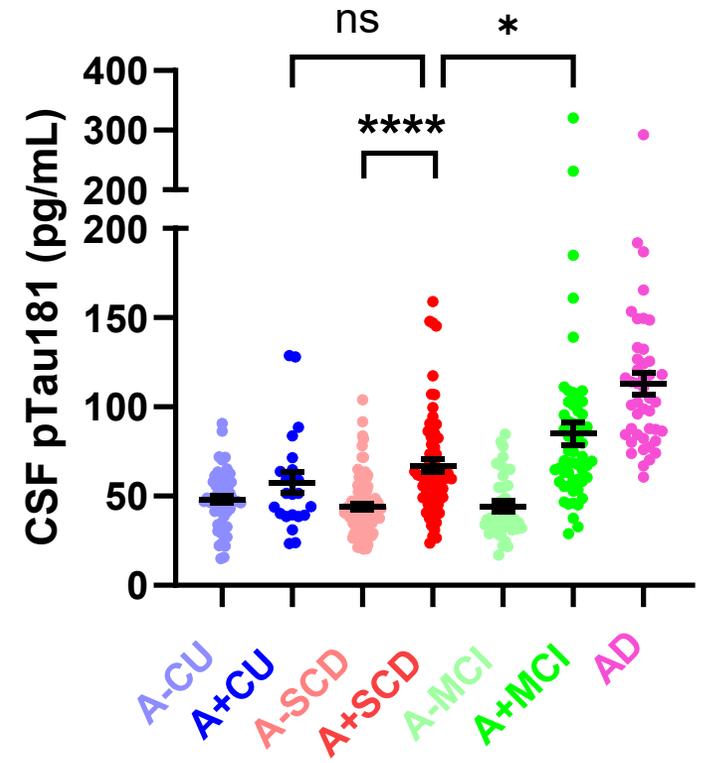
A



B

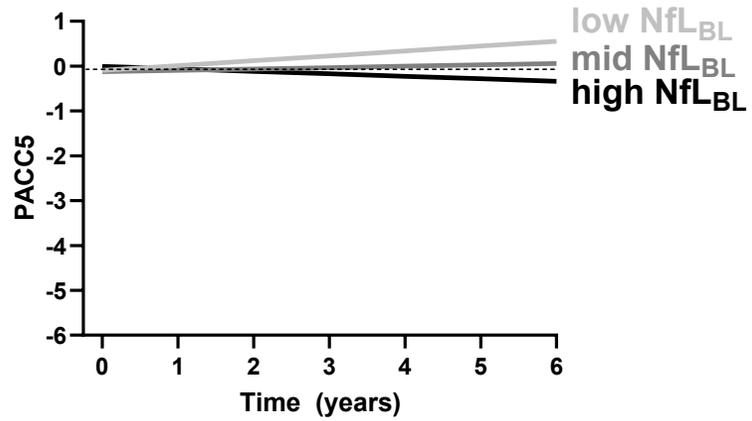


C



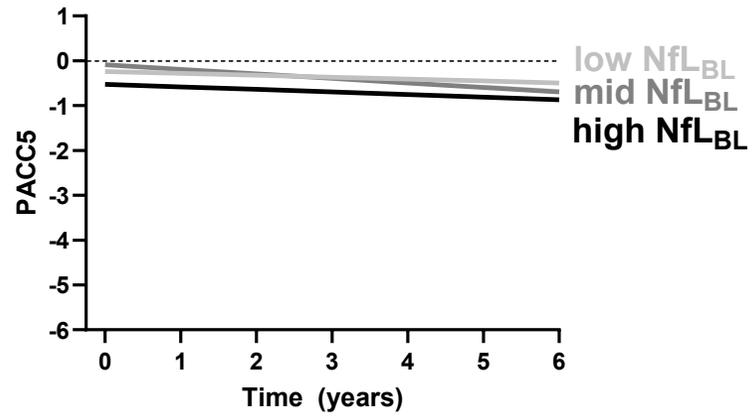
SFigure 2

A A+CU



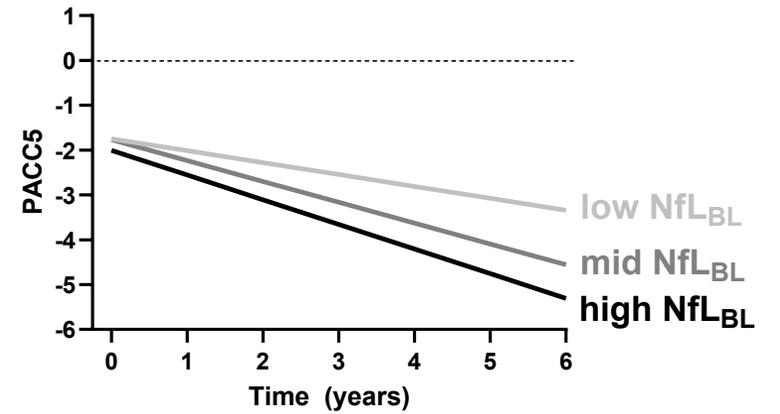
AD stage I

B A+SCD



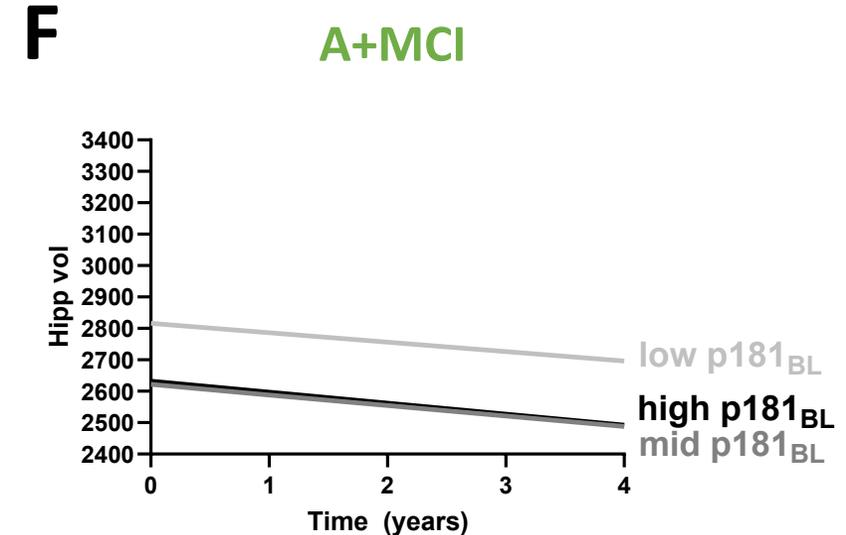
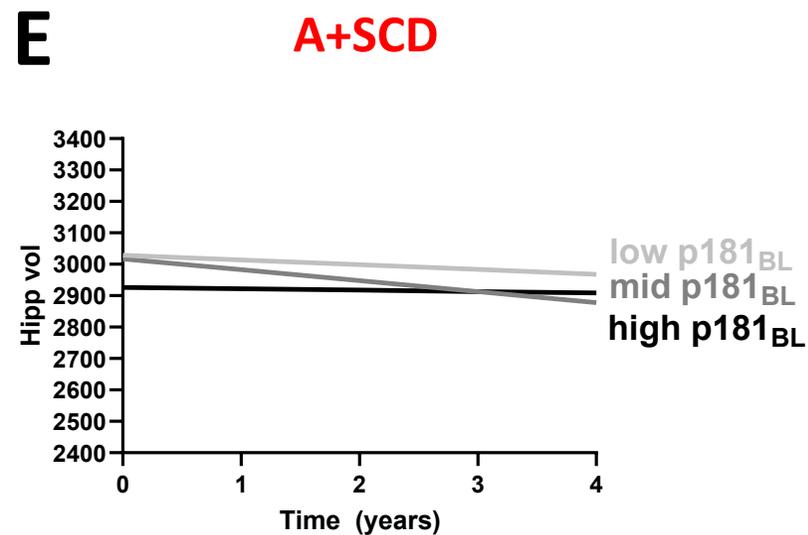
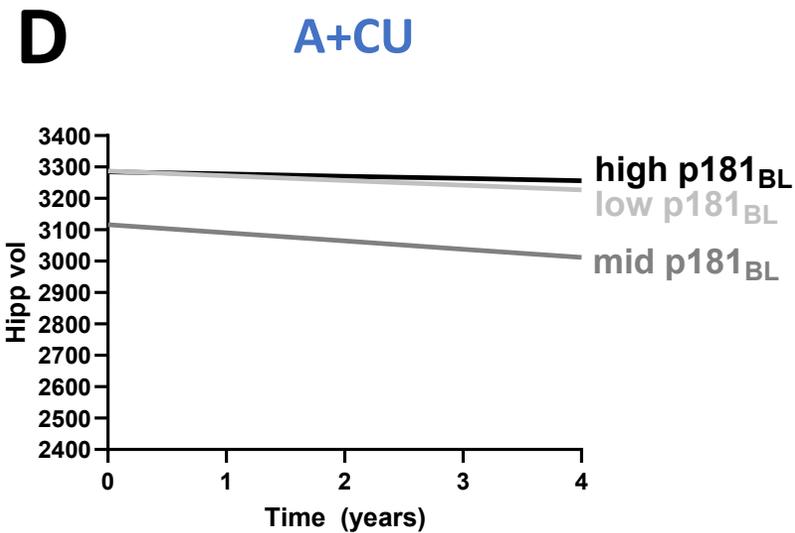
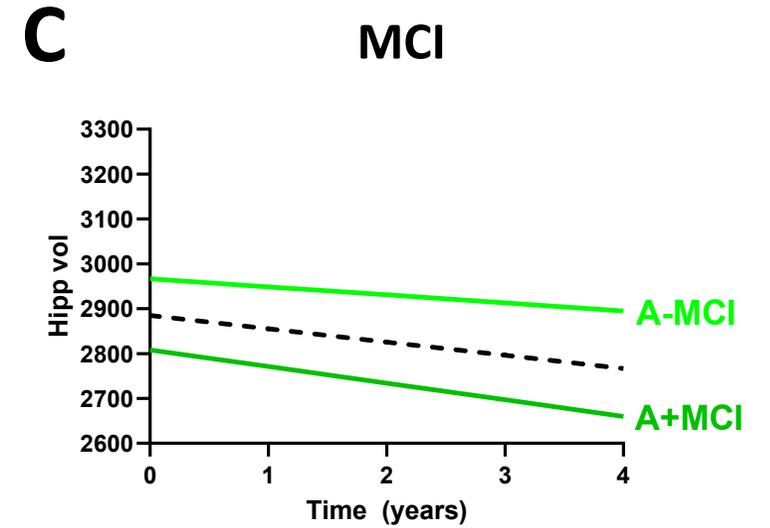
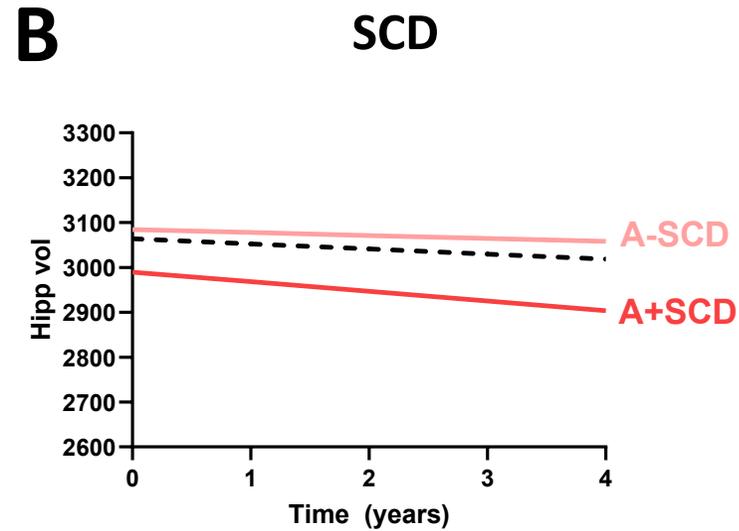
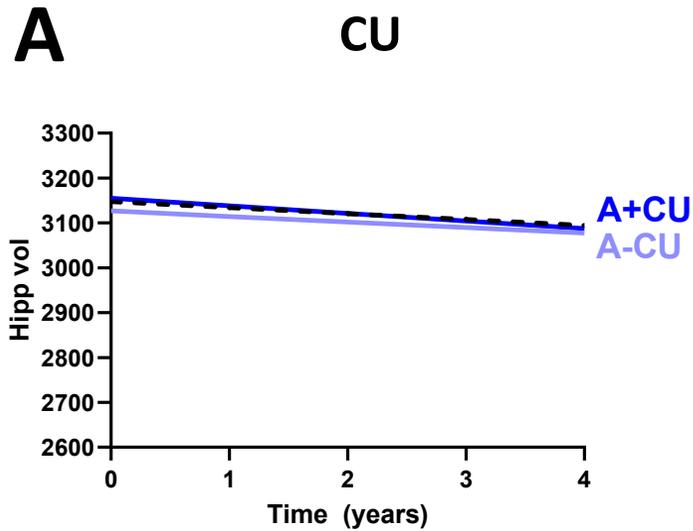
AD stage II

C A+MCI



AD stage III

SFigure 3



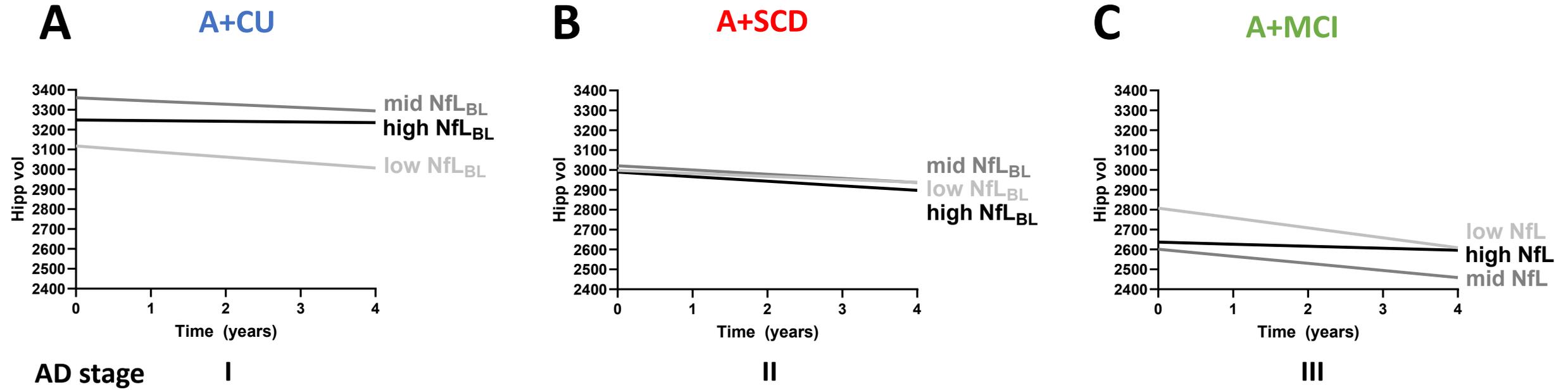
AD stage

I

II

III

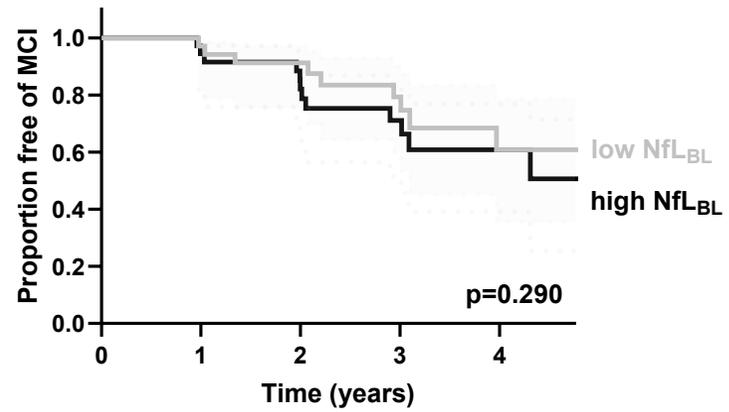
SFigure 4



SFigure 5

A

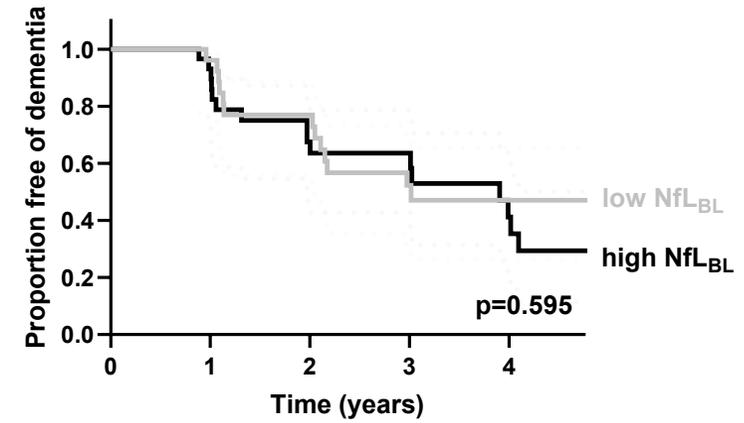
A+SCD → A+MCI



low NfL _{BL}	37	35	31	20	10
high NfL _{BL}	38	34	27	16	8
	at risk (n)				

B

A+MCI → dementia



low NfL _{BL}	27	25	19	11	7
high NfL _{BL}	29	26	17	12	7
	at risk (n)				