

## BIOMARKERS (NON-NEUROIMAGING)

Reduced plasma A $\beta$ 42/40 in individuals with SCD predicts increasing plasma p-Tau 181

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## Abstract

**Background:** In Alzheimer's disease (AD), the decline of plasma A $\beta$ 42/40 occurs before cognitive decline, presenting a potential early screening tool. However, the factors leading to the progression of the disease, specifically the increase in plasma p-Tau 181, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL), remain unclear. This study investigates whether perceived cognitive impairment is associated with downstream biomarker changes in individuals with decreasing A $\beta$ 42/40.

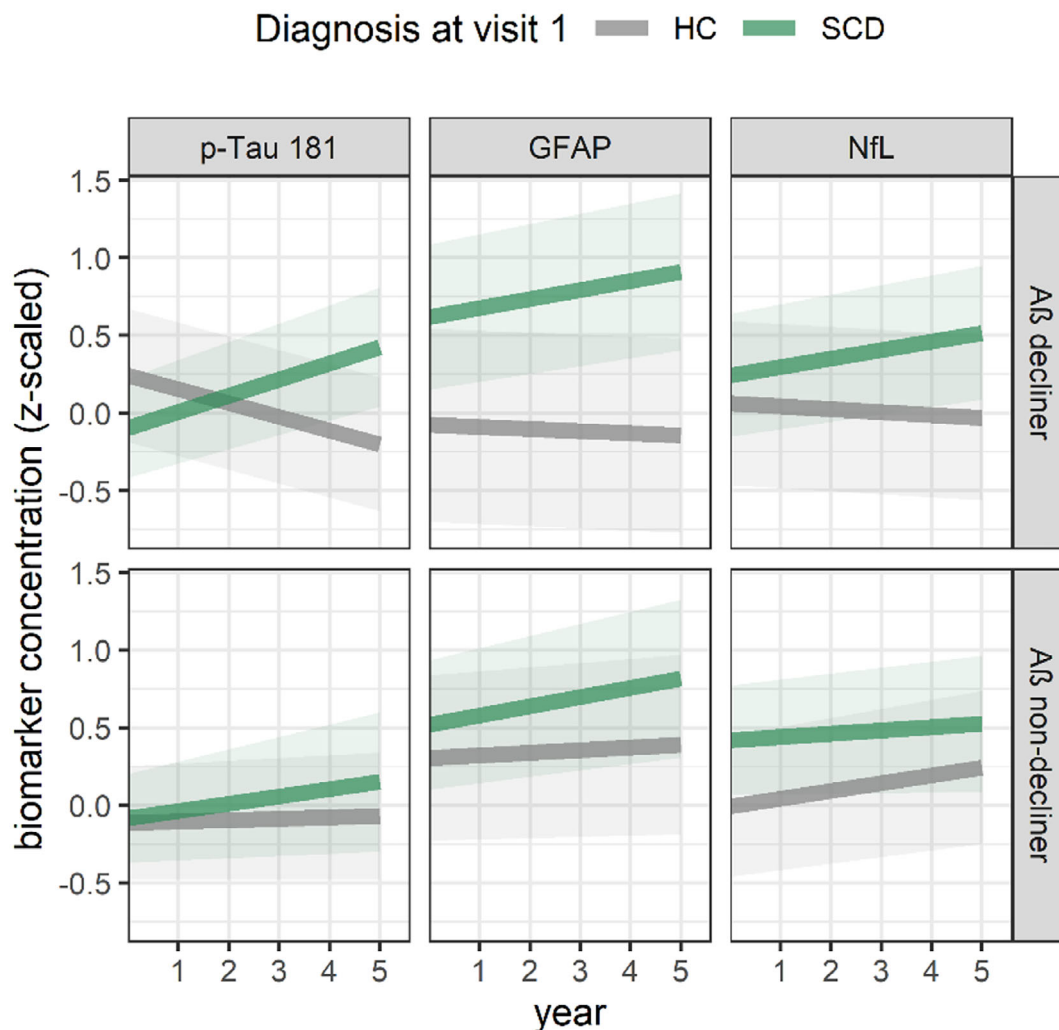
**Method:** Plasma was longitudinally collected from a study population of cognitively healthy controls (HC, n=21) and individuals with subjective cognitive decline (SCD, n=32) for up to five time points over up to five years. Plasma biomarkers were measured using Simoa HD-X (Billerica, USA) with the commercially available kits NEUROLOGY 4-PLEX E and p-Tau 181 advantage kit V2. A 2-means cluster analysis classified the participants as A $\beta$  decliners/non-decliners based on their plasma A $\beta$ 42/40 change (difference between plasma A $\beta$ 42/40 at the first visit and last visit). The self-reported Everyday Cognition (ECOG) and Multifactorial Memory Questionnaire (MMQ) provided two continuous measures of subjective cognition. Using linear mixed models, we examined z-scaled longitudinal plasma p-Tau 181, GFAP and NfL for A $\beta$  decliners and non-decliners with a diagnosis of SCD (model 1), elevated scores in ECOG (model 2) or decreased scores in MMQ (model 3).

**Result:** The cluster analysis separated the participants into A $\beta$  decliners (plasma A $\beta$ 42/40 change=-0.5sd, n=22) and non-decliners (A $\beta$  change=0.2sd, n=31). Model 1 showed a substantial difference in longitudinal p-Tau 181 in A $\beta$  decliners for HC vs. SCD (estimated mean difference=-0.19sd, p<0.001). A yearly increase of plasma p-Tau 181 in A $\beta$  decliners was found only for SCD (0.10sd [0.03; 0.18], p=0.008) but not HC (-0.09sd [-0.17; -0.01], p=0.028) participants. Neither model 2 nor model 3 showed relevant effects of ECOG or MMQ on longitudinal plasma p-Tau 181, GFAP or NfL, in neither A $\beta$  decliners nor non-decliners.

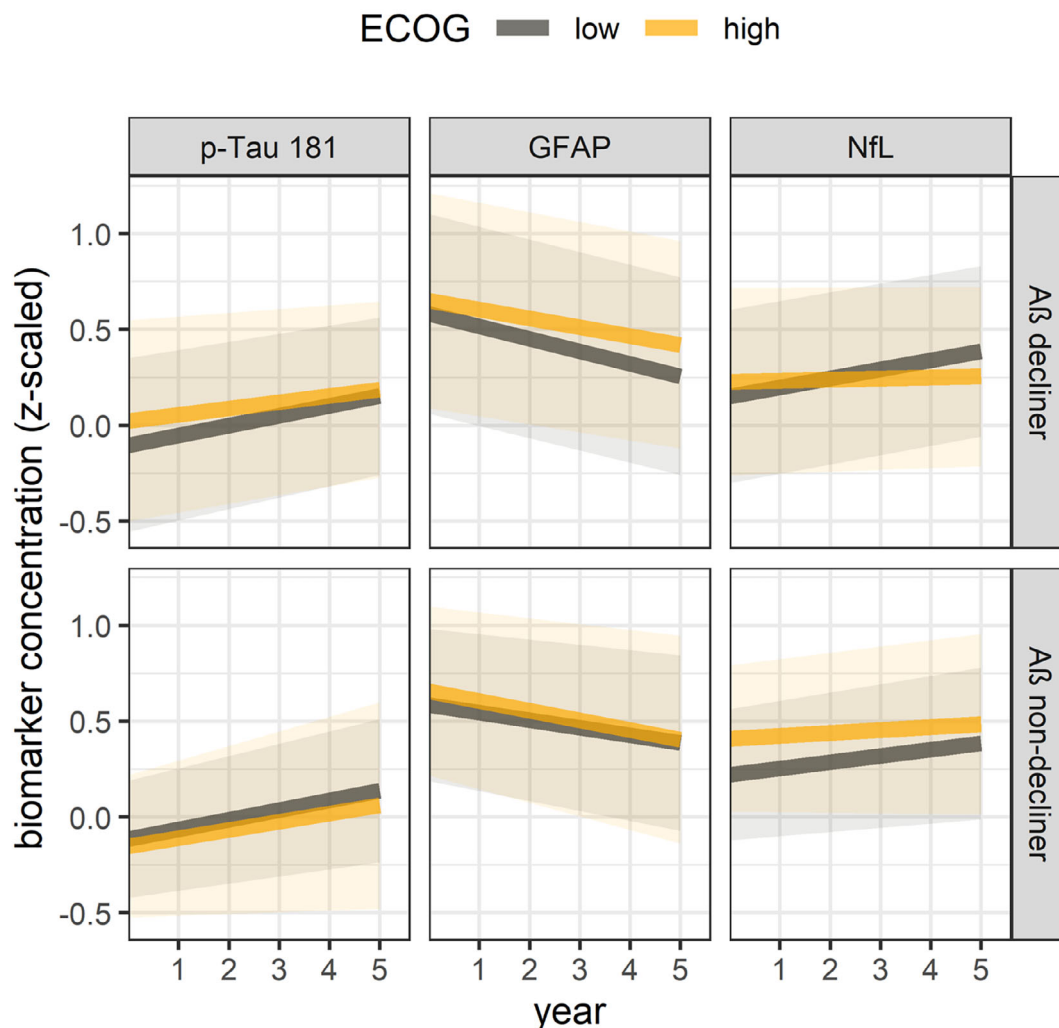
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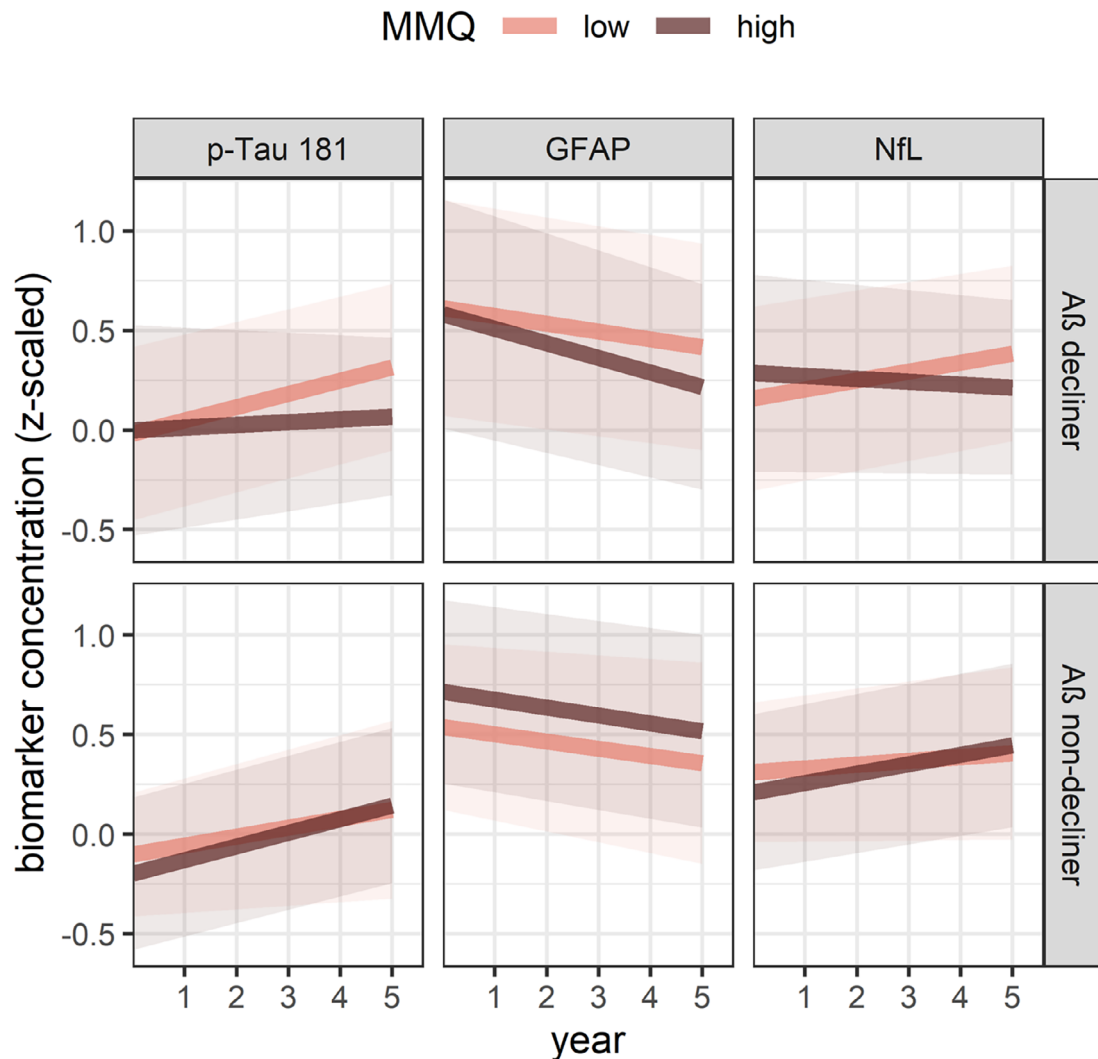
**Conclusion:** Our findings suggest a predictive value of the diagnosis SCD for pathologic progression in participants with declining plasma A $\beta$ 42/40. Our study contributes to a better understanding of early pathological changes of AD and highlights the use for a multi-modal diagnostic approach involving both objective biomarkers and professional evaluation.



**Figure 1: Model 1 showed a substantial difference in longitudinal p-Tau 181 in A $\beta$  decliners for HC vs. SCD (estimated mean difference =  $-0.19sd$ ,  $p < 0.001$ ).** A yearly increase of plasma p-Tau 181 in A $\beta$  decliners was found only for SCD ( $0.10sd$  [ $0.03$ ;  $0.18$ ],  $p = 0.008$ ) but not HC ( $-0.09sd$  [ $-0.17$ ;  $-0.01$ ],  $p = 0.028$ ) participants. Taking HC and SCD together, there was no change for p-Tau 181 in total Abeta decliners ( $0.01sd$  [ $-0.05$ ;  $0.06$ ]). Participants were classified into A $\beta$  decliners/non-decliners by a 2-means cluster analysis based on their difference between A $\beta_{42/40}$  at first visit and last visit (mean difference  $A\beta_{decliner} = -0.5sd$ ,  $n_{A\beta_{decliner}} = 22$ , mean difference  $A\beta_{non-decliner} = 0.2sd$ ,  $n_{A\beta_{non-decliner}} = 31$ ). Longitudinal trajectories were extracted from linear mixed models correcting for age. Abbreviations: A $\beta$  = amyloid beta, CI = confidence interval, GFAP = glial fibrillary acidic protein, HC = healthy control, NfL = neurofilament light chain, p-Tau 181 = tau phosphorylated at threonine 181, SCD = subjective cognitive decline.



**Figure 2: Model 2 showed no effect of ECOG on the association between Aβ decline and p-Tau 181, GFAP or NfL ( $p > 0.05$ ).** Participants were classified into Aβ decliners/non-decliners by a 2-means cluster analysis based on their difference between Aβ42/40 at first visit and last visit (mean difference Aβdecliner =  $-0.5sd$ ,  $n$  Aβdecliner = 22, mean difference Aβnon-decliner =  $0.2sd$ ,  $n$  Aβnon-decliner = 31). ECOG scores were classified into low (ECOG = 1.33) or high (ECOG = 1.98) by a 2-means cluster analysis based on the first available ECOG score for every participant. Longitudinal trajectories were extracted from linear mixed models correcting for age. Abbreviations: Aβ = amyloid beta, ECOG = Everyday cognition questionnaire, GFAP = glial fibrillary acidic protein, NfL = neurofilament light chain, p-Tau 181 = tau phosphorylated at threonine 181, SCD = subjective cognitive decline.



**Figure 3: Model 3 showed no effect of MMQ on the association between Aβ decline and p-Tau 181, GFAP or NfL ( $p > 0.05$ ).** Participants were classified into Aβ decliners/non-decliners by a 2-means cluster analysis based on their difference between Aβ<sub>42/40</sub> at first visit and last visit (mean difference Aβdecliner =  $-0.5sd$ ,  $n$  Aβdecliner = 22, mean difference Aβnon-decliner =  $0.2sd$ ,  $n$  Aβnon-decliner = 31). MMQ scores were classified into low (MMQ = 27.21) or high (MMQ = 49.66) by a 2-means cluster analysis based on the first available ECOG score for every participant. Longitudinal trajectories were extracted from linear mixed models correcting for age. Abbreviations: Aβ = amyloid beta, GFAP = glial fibrillary acidic protein, MMQ = Multifactorial Memory Questionnaire, NfL = neurofilament light chain, p-Tau 181 = tau phosphorylated at threonine 181.