# CSF markers YKL40, sTREM2, and $\alpha$-synuclein enhance the Alzheimer's disease A/T/N criteria to detect early changes in cognition

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Understand how information from CSF biomarkers from the NTK platform can be used in population studies. Investigate cognitive decline in researchers own cohorts using the ATN criteria.

## INTRODUCTION

Alzheimer's disease (AD) is a multifactorial disease including pre-clinical, prodromal and clinical phases. CSF "A/T/N" (Aβ42, pTau181, tTau) biomarkers help characterize the biological state of AD.

The primary aim was to assess contributions of eight CSF markers for predicting changes in cognition.

## METHODS

CSF from 237 participants (CN: 176[74.3%], MCI: 33[13.9%], AD: 28[11.8%]) of the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing was used to measure Aβ42 (GenII assay), pTau181, and tTau (Elecsys® assays; Roche Diagnostics International Ltd, Rotkreuz, Switzerland) along with neurogranin, neurofilament light (NFL), α-synuclein, glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL-40), soluble triggering receptor expressed on myeloid cells-2 (sTREM2), s100 calcium-binding protein B (s100B), and interleukin-6 (IL-6) from the NeuroToolKit (NTK) panel of exploratory prototype assays (all Roche Diagnostics International Ltd).

NTK biomarker concentrations were measured amongst each of four ATN groups at baseline; 1) A-/T-/N- (reference group), 2) A+/T±/N± (amyloid+), 3) A-/T±/N± (amyloid-), and 4) A+/T+/N+.

Change in cognition was assessed using the pre-clinical Alzheimer's cognitive composite (PACC) and the clinical dementia rating sum of boxes (CDR-SB) scores, in all four ATN groups, stratified by low/high NTK biomarker over a minimum of 36 months.

The primary outcome was defined as change in cognition in amyloid+ participants modulated by the addition of NTK markers to ATN groups.
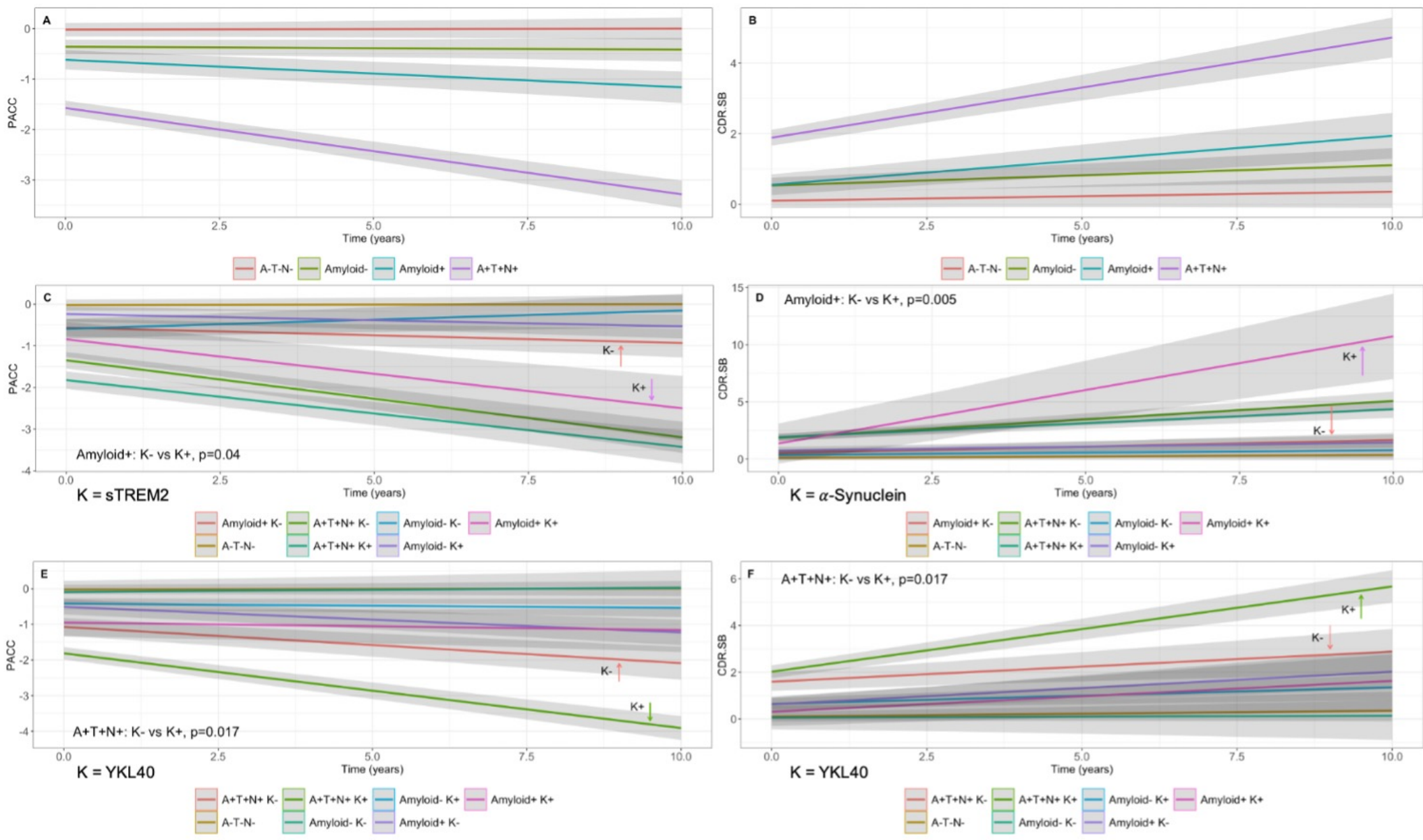
## RESULTS



Figure 1: Rates of change in cognition across A/T/N/K groups. Solid lines represent the slope derived from linear mixed effects models (LMM's). Grey shaded area's represent the 95%CI of the slope as derived from LMM. Slope for K- & K+ represents the rate of change as calculated for participants with low & high NTK biomarker values within the ATN subgroup respectively. PACC: pre-clinical cognitive composite; CDR-SB: Clinical dementia rating sum of boxes; sTREM2: soluble triggering receptor expressed on myeloid cells 2; YKL40: chitinase-3-like protein 1.
A) Differential slopes of cognitive decline for the PACC score between ATN groups; B) Differential slopes of cognitive decline as marked by increases in the CDR-SB over time between ATN groups; C) Differential slopes of cognitive decline for the PACC score between ATNK groups, whereby K represents sTREM2; D) Differential slopes of cognitive decline as marked by increases in the CDR-SB over time between ATNK groups whereby K represents α-Synuclein; E) Differential slopes of cognitive decline for the PACC score between ATNK groups, whereby K represents YKL40; F) Differential slopes of cognitive decline as marked by increases in the CDR-SB over time between ATNK groups whereby K represents YKL40.

A+/T+/N+ participants had faster cognitive decline on both PACC and CDR-SB over time compared to all other groups (Figure 1A, PACC; Figure 1B, CDR-SB). Within the amyloid+ group, participants with high sTREM2 (K+) had a faster rate of decline in PACC compared to those with low sTREM2 (K-, p=0.04; Figure 1C), whilst participants with high α-synuclein had a faster increase in CDR-SB compared with those with low α-synuclein (p=0.005; Figure 1D). Amongst participants who were A+/T+/N+, those with high YKL40 had a significantly faster rate of decline in PACC (p=0.017; Figure 1E), and a faster increase in CDR-SB, (p=0.017; Figure 1F) compared with those who with low YKL40.

## CONCLUSIONS

Biomarkers of microglial activation (sTREM2), synaptic function and synuclein metabolism (α-synuclein), and astrocytic activation (YKL-40) may be appropriate to discern rates of cognitive change within amyloid+ participants. Findings are being validated in a separate population.

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