High CSF *tau* is related to reduced hippocampal volume and subjective cognitive decline in healthy elderly with amyloid pathology

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BACKGROUND AND OBJECTIVES

In preclinical stages of Alzheimer's disease (AD), questions remain about relationships between cerebrospinal fluid (CSF) amyloid beta (Aß) and *tau* proteins, and other markers of AD pathogenesis. In the PREVENT-AD cohort of cognitively normal older adults with a parental history of AD-like dementia, we assessed CSF Aß and *tau* in relation to brain integrity and cognitive function.

METHODS

Cohort

Cognitively normal older adults with a family history of AD

n=105	Age (years)	Male (%)	Education (years)
	63±5	29	15±3

CSF Measurements

Amyloid-beta 42 and 40 (AB_{1-42} and AB_{1-40}), phosphorylated tau (P-*tau*)

Neuroimaging

Hippocampal volume adjusted for total intracranial volume

Cognition

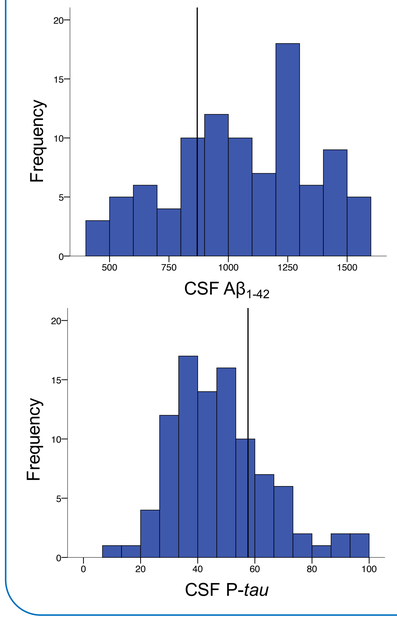
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total score

- Subjective cognitive decline: Self-reported change in memory compared to 20 years ago

Statistical analyses

General linear models with age as a covariate

DISTRIBUTIONS OF CSF Aβ AND P-*tau*

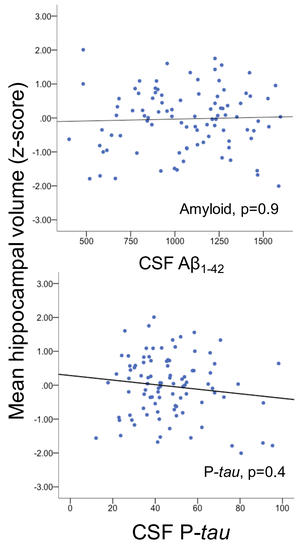


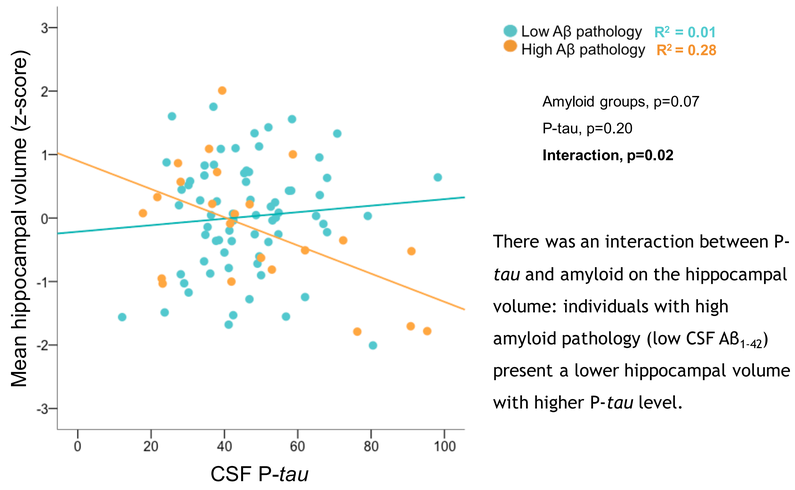
Cutoff at the 25th percentile

High Aß pathology:
CSF AB_{1-42}<845

Low Aß pathology:
CSF AB_{1-42}>845

RELATIONSHIPS BETWEEN HIPPOCAMPAL VOLUME AND CSF MARKERS

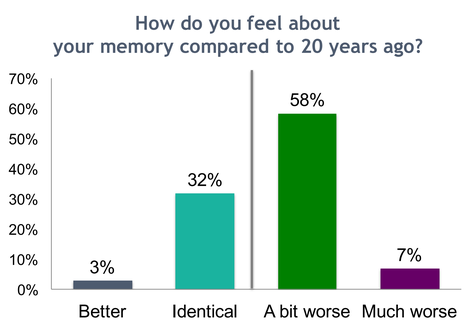


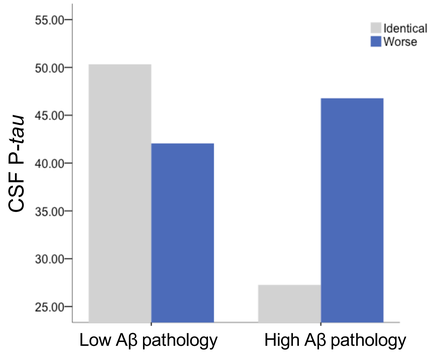


There was an interaction between P-*tau* and amyloid on the hippocampal volume: individuals with high amyloid pathology (low CSF AB_{1-42}) present a lower hippocampal volume with higher P-*tau* level.

RELATIONSHIPS BETWEEN COGNITION AND CSF MARKERS

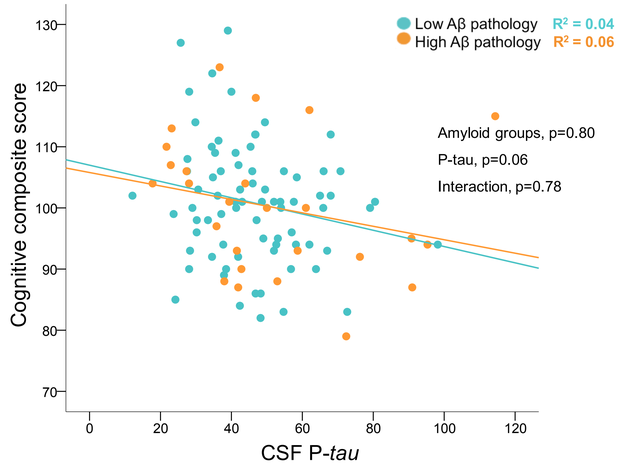
SUBJECTIVE COGNITIVE DECLINE





Binary logistic regression: High amyloid pathology is associated (p=0.05) with reporting worsening of one's memory compared to 20 years ago.

OBJECTIVE COGNITIVE SCORE



There was no interaction between Aß groups and P-*tau* on cognitive performance, although total RBANS score declines with elevated P-*tau* at trend level.

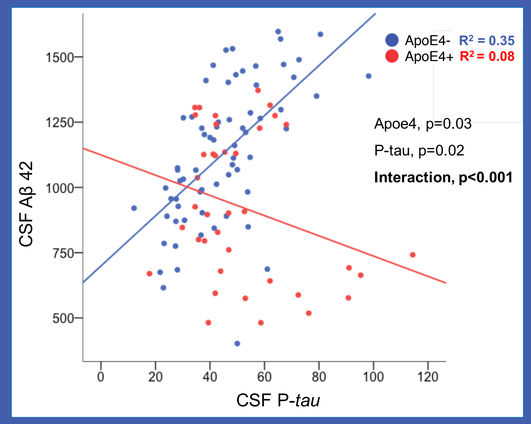
CONCLUSIONS

There are already detectable relations between CSF biomarkers, hippocampal volume and subjective cognitive decline in cognitively normal, asymptomatic elderly, driven mainly by individuals with high P-*tau* and low Aß1-42 levels.

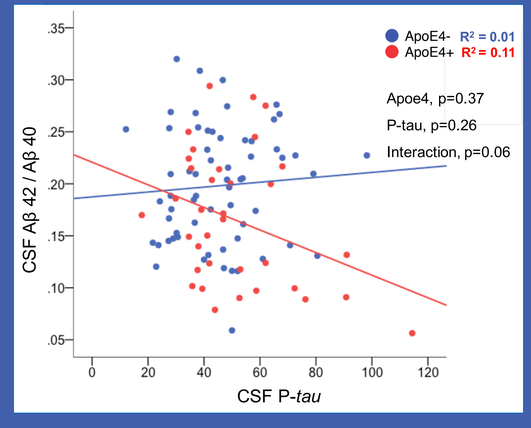
FUTURE WORK

Recent literature suggests that the ratio of CSF Aß42/Aß40 might be more sensitive to AD pathology (Janelidze et al., *Annals Clin Transl Neurol*, 2016) and predict better amyloid accumulation in the brain over to years (Racine et al., *Alzheimer's and Dementia*, 2016) than Aß42 alone. We are starting to investigate the effects of using such a ratio in our analyses.

Specifically, we looked at the difference between the relationships of amyloid and P-*tau*, using either CSF Aß42 or Aß42/ Aß40.



The association between levels of Aß and P-*tau* was clearly dependent on APOE-*ε*4 status (interaction p<0.001). In *ε*4 carriers, we observed an expected relationship of higher Aß pathology (lower CSF values) with higher P-*tau*, but the inverse was found in non-carriers.



When using the ratio Aß42/Aß40, the previous interaction is not significant anymore, but we still observed the same relationship in *ε*4 carriers.