

# CSF Synaptic Biomarkers in the Preclinical Stage of Alzheimer Disease and Their Association With MRI and PET

## A Cross-sectional Study

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on behalf of the ALFA Study

Cite as: *Neurology*® 2021;97:e2065-e2078. doi:10.1212/WNL.0000000000012853

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### Study Question

Are CSF synaptic biomarkers altered in the early preclinical stage of Alzheimer disease (AD)?

### What Is Known and What This Paper Adds

While synaptic dysfunction and alterations in the levels of associated CSF biomarkers are a known feature in symptomatic patients with AD, evidence on their levels in early preclinical stages of the disease are limited. This study reveals an increase in CSF synaptic biomarkers in preclinical AD and potential associations with other known risk factors. The current study sheds light on the elevated status of CSF biomarkers in early AD that also correlate with A $\beta$  and tau pathologies.

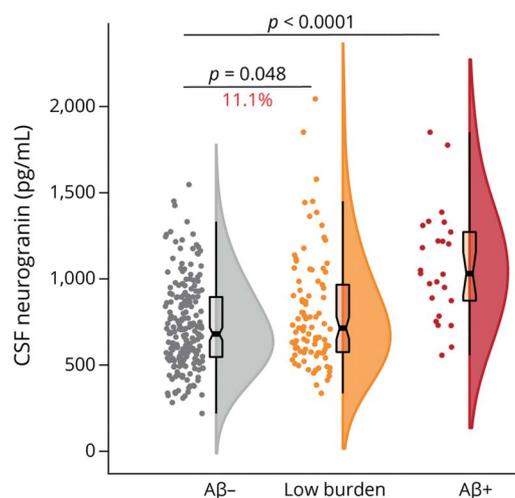
### Methods

The ALFA (Alzheimer's and Families) study enrolled middle-aged, cognitively unimpaired individuals enriched for family history of AD (47.4%) and APOE- $\epsilon$ 4 carriership (32.5%). Data from this nested analysis came from 397 people enrolled in the ALFA + cohort who participated based on their specific AD risk profile, determined by participants' AD parental history and APOE status, verbal episodic memory score, and CAIDE score. A detailed phenotyping was performed in ALFA + participants, including measurement of CSF biomarkers, a structural MRI, and fluorodeoxyglucose and A $\beta$  PET imaging. CSF biomarkers were measured using immunoassays (A $\beta$ 40, A $\beta$ 42, GAP-43, neurogranin, neurofilament light chain/NfL, p-tau, and t-tau) and immunoprecipitation mass spectrometry (SNAP-25 and synaptotagmin-1). To study very early changes in the continuum, the following 3 groups were defined based on both CSF and PET A $\beta$  status: (i) CSF/PET A $\beta$ -negative (negative CSF A $\beta$ 42/40 and A $\beta$  PET < 30 Centiloids), (ii) group with low burden of A $\beta$  pathology (positive CSF A $\beta$ 42/40 but A $\beta$  PET < 30 Centiloids), and (iii) CSF/PET A $\beta$ -positive (positive CSF A $\beta$ 42/40 and A $\beta$  PET  $\geq$  30 Centiloids).

### Results and Study Limitations

All measured CSF biomarkers increased with age. CSF neurogranin was higher in females, and CSF SNAP-25 was higher in APOE- $\epsilon$ 4 carriers. CSF biomarker levels were associated with A $\beta$  load. Furthermore, CSF neurogranin, SNAP-25, GAP-43, and synaptotagmin-1 were significantly increased in participants with a low burden of A $\beta$ , suggesting an association with early AD pathogenesis. Similarly, increased biomarker levels were associated with increased CSF p-tau, which was independent of A $\beta$ . On analyzing the

**Figure** CSF Synaptic Biomarkers Were Compared Between Groups



CSF/PET A $\beta$ -negative group (gray), low burden group (yellow), and CSF/PET A $\beta$ -positive group (red).

association of CSF biomarkers with neurodegeneration markers, CSF neurogranin and GAP-43 were significantly associated with changes in brain metabolism and cortical thickness. A limitation of the study is that not all synaptic biomarkers were included. Also, changes over time have not been predicted.

### Registration, Study Funding, and Competing Interests

The study was funded by la Caixa Foundation, the Alzheimer's Association, and an international anonymous charity foundation through the TriBEKa Imaging Platform project. This study was registered at clinicaltrials.gov (NCT02485730). The authors report no competing interests. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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*Neurology* 2021;97:e2065-e2078 Published Online before print September 23, 2021

DOI 10.1212/WNL.0000000000012853

**This information is current as of September 23, 2021**

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