Supplementary Material

Cohort characteristics

The BioFINDER-2 study enrolls participants in five sub-cohorts (NCT03174938). Sub-cohorts 1 and 2 include neurologically and cognitively healthy elderly subjects, who were required to: a) be 45-65 years old (sub-cohort 1) or 66-100 years old (sub-cohort 2); b) not have cognitive symptoms as assessed by a physician specialized in cognitive disorders; c) have a MMSE score between 27-30; d) do not fulfill the criteria for mild or major neurocognitive disorder (MCI or dementia) according to DSM-51; and e) be fluent in Swedish.[1] The recruitment process of this cohort was designed to have 50% apolipoprotein E ε4 carriers.

Sub-cohort 3 comprises participants with subjective cognitive decline (SCD) or MCI, who were required to: a) be 40-100 years old; b) referred to the memory clinics due to cognitive symptoms; c) have a MMSE score of 24-30 points; d) do not fulfill the criteria for any dementia (major neurocognitive disorder) according to DSM-51, e) be fluent in Swedish. In accordance with the research framework by the National Institute on Aging-Alzheimer's Association (Jack et al., 2018a), study participants with SCD were considered to be cognitively unimpaired. Participants were classified as having MCI if they performed worse than -1.5 standard deviations in any cognitive domain according to age and education stratified test norms.

Sub-cohort 4 consists of participants with dementia due to AD, who were required to: a) be 40-100 years old; b) be referred to the memory clinics due to cognitive symptoms; c) have a MMSE score of ≥ 12 points; d) fulfill the DSM-5 criteria for dementia (major neurocognitive disorder) due to Alzheimer disease; and e) be fluent in Swedish. Clinical AD dementia was diagnosed according to the DSM-5 criteria for major neurocognitive disorder due to AD. All AD patients were Aβ-positive in agreement with the updated NIA-AA criteria for AD.[2]

Sub-cohort 5 covers other non-AD neurodegenerative disorders. Inclusion criteria were: a) ages 40-100 years; b) fulfillment of criteria for dementia (major neurocognitive disorder) due to frontotemporal dementia, unspecified dementia, amyotrophic lateral sclerosis, dementia with Lewy bodies, Parkinson's disease with

dementia (PD), subcortical vascular dementia, PD, progressive supranuclear palsy, semantic dementia or semantic variant primary progressive aphasia; and c) be fluent in Swedish.

Exclusion criteria for all sub-cohorts were: a) having significant unstable systemic illness that makes it difficult to participate in the study; b) current significant alcohol or substance misuse; and c) refusing lumbar puncture, MRI or PET.

The Regional Ethical Review Board of Lund University, the Swedish Medicines and Products Agency, and the Radiation Safety Committee of Skåne University Hospital in Sweden approved the study and written, informed consent was obtained from all participants according to the Declaration of Helsinki.

Correlations between different plasma GFAP and CSF GFAP assays in the BioFINDER-1 cohort

In order to ensure that the two different assays used to determine the concentrations of plasma GFAP (Simoa) and CSF GFAP (Elecsys) did not measure very different variants of this marker, we conducted an additional analysis in BioFINDER-1 where we had plasma GFAP values measured both with Simoa and the Elecsys assays as well as CSF GFAP measured with the Elecsys assay. This sample included 330 individuals, of which 208 subjects were cognitively unimpaired and 122 were cognitively impaired. The details about the study design and characteristics of the BioFINDER-1 cohort can be found elsewhere.[3] In brief, cognitively normal subjects were required to have a Clinical Dementia Rating score of 0, 27–30 points on the Mini-Mental State Examination, not fulfill criteria for mild cognitive impairment or dementia, have no history of cognitive change over time, and be fluent in Swedish. Cognitively impaired subjects were required to fulfill the DSM-5 criteria for mild neurocognitive disorder or major neurocognitive disorder due to Alzheimer's disease.[4]

The analyses conducted in the BioFINDER-1 cohort showed that there was a strong correlation between Simoa plasma GFAP and Elecsys plasma GFAP ($r = 0.879$, $p < 0.001$) levels (Supplementary Figure 1A). Moreover, the correlation between Simoa plasma GFAP and Elecsys CSF GFAP ($r = 0.519$, $p < 0.001$) (Supplementary Figure

1B) was very similar to the one between Elecsys plasma GFAP and Elecsys CSF GFAP ($r = 0.574$, $p < 0.001$) (Supplementary Figure 1C). Altogether, these findings indicate that the different assays used to determine plasma GFAP and CSF GFAP in our main analyses in the BioFINDER-2 cohort did not measure very different isoforms of GFAP.

Correlations between all biomarkers

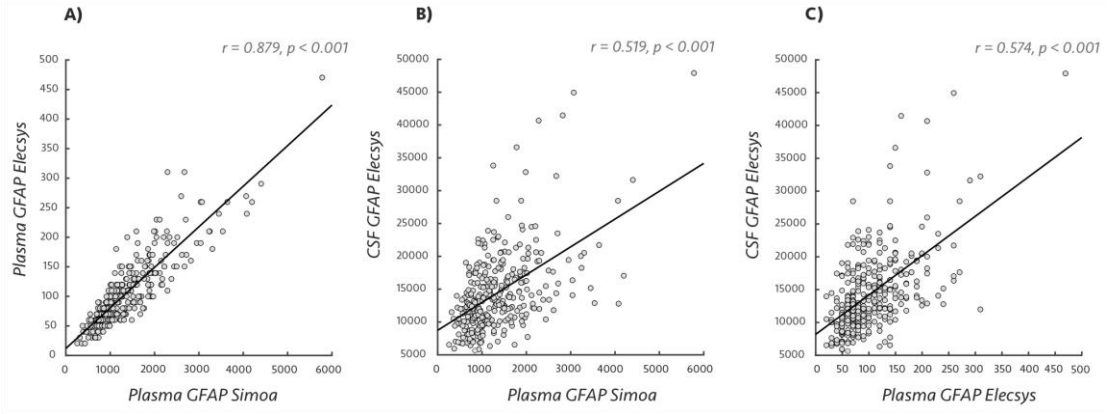
There were significant correlations between plasma GFAP, CSF GFAP, CSF sTREM2 and CSF YKL-40 in the whole sample and in all CU individuals (Supplementary Table 1). In CI individuals, similar results were observed, except for the correlation between plasma GFAP and CSF sTREM2, which was no longer significant ($R = 0.116$, $p = 0.173$) (Supplementary Table 1). Finally, in non-AD patients, all correlations were significant except the ones between plasma GFAP and CSF sTREM2 ($R = 0.026$, $p = 0.827$) as well as between plasma GFAP and CSF YKL-40 ($R = 0.120$, $p = 0.306$) (Supplementary Table 1). The lack of significant correlations between some of the markers in the CI and non-AD groups could be due to the smaller sample sizes in these groups (CI = 141; non-AD = 75) compared to the whole sample (n = 504) and all CU individuals (n = 288) and the fact that the correlations between plasma GFAP with CSF sTREM2 and YKL-40 were in general weaker than the ones between plasma GFAP and CSF GFAP or between all biomarkers measured in the CSF.

Supplementary Table 1. Correlations between biomarkers in different groups

Whole sample	Plasma GFAP	CSF GFAP	CSF sTREM2
CSF GFAP	R = 0.607 (P < 0.001)	-	-
CSF sTREM2	R = 0.244 (P < 0.001)	R = 0.538 (P < 0.001)	-
CSF YKL-40	R = 0.370 (P < 0.001)	R = 0.642 (P < 0.001)	R = 0.631 (P < 0.001)
All CU	Plasma GFAP	CSF GFAP	CSF sTREM2
CSF GFAP	R = 0.659 (P < 0.001)	-	-
CSF sTREM2	R = 0.328 (P < 0.001)	R = 0.557 (P < 0.001)	-
CSF YKL-40	R = 0.403 (P < 0.001)	R = 0.641 (P < 0.001)	R = 0.661 (P < 0.001)
All CI	Plasma GFAP	CSF GFAP	CSF sTREM2
CSF GFAP	R = 0.558 (P < 0.001)	-	-
CSF sTREM2	R = 0.116 (P = 0.173)	R = 0.466 (P < 0.001)	-
CSF YKL-40	R = 0.342 (P < 0.001)	R = 0.636 (P < 0.001)	R = 0.643 (P < 0.001)
Non-AD	Plasma GFAP	CSF GFAP	CSF sTREM2
CSF GFAP	R = 0.360 (P < 0.001)	-	-
CSF sTREM2	R = 0.026 (P = 0.827)	R = 0.526 (P < 0.001)	-
CSF YKL-40	R = 0.120 (P = 0.306)	R = 0.480 (P < 0.001)	R = 0.435 (P < 0.001)

Data presented in the table correspond to Pearson correlations followed by (p values). CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase 3-like 1.

Supplementary Figure 1. Correlations between different plasma GFAP and CSF GFAP assays in the BioFINDER-1 cohort



Correlation analyses between different plasma and CSF GFAP markers in 330 individuals from the BioFINDER-1 cohort. These analyses showed a strong association between plasma GFAP measured with the Elecsys assay and plasma GFAP measured with the Simoa assay ($r = 0.879$, $p < 0.001$) (A). Moreover, we also found a similar correlation between CSF GFAP measured with the Elecsys assay with both plasma GFAP markers measured with Simoa ($r = 0.519$, $p < 0.001$) (B) and Elecsys assays ($r = 0.574$, $p < 0.001$) (C). CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein. The values in the plot are in pg/mL units.

References

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4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: diagnostic and statistical manual of mental disorders. 5th edn. Arlington, VA: American Psychiatric Association; 2013.