Received: 15 September 2023 | Accepted: 24 January 2024

DOI: 10.1002/dad2.12556

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Association of CSF biomarkers with MRI brain changes in Alzheimer's disease

Nazib M Seidu[1] | **Silke Kern**[1,2] | **Simona Sacuiu**[1,2,3,4] | **Therese Rydberg Sterner**[1,5] | **Kaj Blennow**[6,7] | **Henrik Zetterberg**[6,7,8,9,10,11] | **Olof Lindberg**[3] | **Daniel Ferreira**[3,12] | **Eric Westman**[3,13] | **Anna Zettergren**[1] | **Ingmar Skoog**[1,2]

[1]Neuropsychiatric Epidemiology (EPINEP), Centre for Ageing and Health (AGECAP), Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Department of Psychiatry Cognition and Old Age Psychiatry, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden

[3]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden

[4]Cognitive Disorders Clinic, Theme Inflammation and Aging, Karolinska University Hospital, Stockholm, Sweden

[5]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden

[6]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[7]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden

[8]UK Dementia Research Institute at UCL, London, UK

[9]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[10]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

[11]UW Department of Medicine, School of Medicine and Public Health, Madison, Wisconsin, USA

[12]Facultad de Ciencias de la Salud, Universidad Fernando Pessoa Canarias, Las Palmas, Spain

[13]Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Correspondence
Nazib M Seidu, Neuropsychiatric Epidemiology (EPINEP), Centre for Ageing and Health (AGECAP), Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Wallinsgatan 6, 431 41 Gothenburg, Sweden.
Email: nazib.m.seidu@gu.se

Funding information
Swedish state under the agreement between the Swedish government and the county councils, Grant/Award Numbers: ALF 716681, ALF-965812; the Swedish Research Council, Grant/Award Numbers: 2012-5041, 2015-02830, 2019-01096, 2013-8717, 2017-00639, 2022-00882; Alzheimer Drug Discovery Foundation (ADDF), Grant/Award Number: #RDAPB-201809-2016615; Swedish Alzheimer Foundation, Grant/Award Numbers: #AF-930351, #AF-939721, #AF-968270;

Abstract

The relation between cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) and magnetic resonance imaging (MRI) measures is poorly understood in cognitively healthy individuals from the general population. Participants' (n = 226) mean age was 70.9 years (SD = 0.4). CSF concentrations of amyloid beta (Aβ)1-42, total tau (t-tau), phosphorylated tau (p-tau), neurogranin, and neurofilament light, and volumes of hippocampus, amygdala, total basal forebrain (TBF), and cortical thickness were measured. Linear associations between CSF biomarkers and MRI measures were investigated. In Aβ1-42 positives, higher t-tau and p-tau were associated with smaller hippocampus (P = 0.001 and P = 0.003) and amygdala (P = 0.005 and P = 0.01). In Aβ1-42 negatives, higher t-tau, p-tau, and neurogranin were associated with larger TBF volume (P = 0.001, P = 0.001, and P = 0.01). No associations were observed between the CSF biomarkers and an AD signature score of cortical thickness. AD-specific biomarkers in cognitively healthy 70-year-olds may be related to TBF, hippocampus,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Authors. *Alzheimer's & Dementia:* Diagnosis, Assessment & Disease Monitoring published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

Hjärnfonden, Sweden, Grant/Award Numbers: #FO2017-0243, #ALZ2022-0006; National Institute of Health, USA, Grant/Award Number: #1R01AG068398-01; Alzheimer's Association 2021 Zenith Award, Grant/Award Number: ZEN-21-848495

and amygdala. Lack of association with cortical thickness might be due to early stage of disease.

KEYWORDS
Alzheimer's disease, amygdala, amyloid beta 1-42, cognitively healthy, cerebrospinal fluid biomarkers, cortical Alzheimer's disease signature score, hippocampus, magnetic resonance imaging measures, neurofilament light protein, neurogranin, phosphorylated tau, total basal forebrain, total tau

1 | INTRODUCTION

Alzheimer's disease (AD) is the cause for the most common type of dementia, accounting for > 60% of all dementia cases globally.[1] In the cerebrospinal fluid (CSF), AD is characterized by reduced levels of amyloid beta ($A\beta_{1\text{-}42}$ and elevated levels of total tau (t-tau) and phosphorylated tau (p-tau).[2] We recently reported that 46% of cognitively healthy 70-year-olds had pathologic AD markers in CSF (Aβ42, t-tau, and/or p-tau).[3] According to the amyloid cascade hypothesis,[4] amyloid accumulation is the first step of AD. The hypothetical model by Jack et al. suggests that abnormal changes of Aβ42 levels in CSF are the first sign of AD, followed by accumulation of Aβ on positron emission tomography (PET).[5] Both t-tau and p-tau in CSF are downstream markers of neurodegeneration and tau pathology, after which hypometabolism on [18F]fluorodeoxyglucose-PET (FDG-PET) and structural changes on magnetic resonance imaging (MRI), reflecting neurodegeneration, start to occur.[5] Dementia comes later in the process.

More recently, other CSF biomarkers (i.e., neurogranin [Ng] and neurofilament light [NfL] protein) of potential importance for AD have emerged.[6] Ng is a synaptic protein and therefore a candidate biomarker of synaptic dysfunction, exclusively expressed in brain regions typically affected in AD.[6] NfL is a marker of subcortical large-caliber axonal degeneration that has been associated with multiple neurodegenerative diseases, including AD.[6]

Volumetric reductions in the hippocampus and amygdala, and thinning in AD-vulnerable cortical regions (e.g., entorhinal, middle temporal, inferior temporal, and fusiform cortex) are the best-established early structural MRI markers for staging atrophy and thereby monitoring the progression of AD.[7–9] Neurodegeneration in the basal forebrain is also a typically early change in AD.[10]

The most common finding in previous studies on the relation between CSF or PET biomarkers and cortical integrity among cognitively healthy individuals is the association between Aβ levels (i.e., lower Aβ42 in CSF; higher Aβ accumulation at PET brain imaging) and thinner or lower volume of the cortex.[8,11–19] When it comes to the hippocampus and amygdala, the most common finding reported was the association between biomarkers levels (i.e., lower Aβ42, higher t-tau, p-tau, and NfL in CSF; higher Aβ accumulation at PET brain imaging) and smaller volume,[13,18,20–26] while previous studies including the basal forebrain found associations between elevated Aβ based on PET and smaller volumes.[27,28]

Most previous studies on the association between AD biomarkers and brain measures in cognitively healthy individuals have focused on Aβ and to some extent tau, about cortical integrity and hippocampal volume.[8,11,13,17–24,26] However, few studies have included other biomarkers of relevance (such as Ng and NfL) or tested associations with volumes of the amygdala and the total basal forebrain (TBF). Moreover, few previous studies have used representative population-based samples, and none has included an age-homogeneous group.[18] Hence, the relation between biomarkers of AD and neurodegeneration and changes in AD-related brain regions, before the manifestation of clinical dementia symptoms in older individuals from the general population, has not been fully investigated. This study aimed to investigate relations between the CSF biomarkers of Aβ42, t-tau, p-tau, Ng, and NfL, and early AD-related MRI measures (i.e., hippocampus, amygdala, and TBF volumes, and a cortical AD signature score) in cognitively healthy 70-year-olds recruited within the frame of the population-based H70 studies in Gothenburg, Sweden.[29] Associations were tested in the total sample and after stratification based on Aβ42 pathology, as lower CSF Aβ42 is supposed to be the first change in AD, while tau and other pathology come later downstream in the process. Thus, our theory was that tau and other pathology would probably be more related to MRI findings in the group with amyloid pathology than in the group without amyloid pathology.

2 | MATERIAL AND METHODS

2.1 | Subjects

Participants in this study are part of the Gothenburg H70 Birth Cohort Studies in Sweden, examined between 2014 and 2016.[29] Every 70-year-old in Gothenburg, Sweden, born during 1944 on prespecified birthdates was invited to the examination between 2014 and 2016. One thousand two hundred three ($N = 1203$) individuals participated (response rate 72.2%), and of these 430 (35.8%) consented to a lumbar puncture (LP) conducted between January 14, 2014 and October 19, 2016. Contraindications to LP (anticoagulant, immune modulation, and cancer therapies) were present in 108, leaving 322 individuals who completed LP.[3] For this study, we only included participants with a Clinical Dementia Rating (CDR) score of 0 ($n = 259$), considered cognitively healthy.[3]

Structural MRI were performed on 791 individuals (414 women and 377 men)[29] between April 5, 2014 and September 29, 2016 and for the current study data from 788 individuals with valid MRI measures were extracted from the hive database system.[30] Two hundred fifty nine (n = 259) cognitively healthy individuals had both CSF biomarkers and MRI data. Thirty-three (n = 33) participants were excluded due to failed MRI quality control. The final sample included 226 cognitively healthy individuals with both CSF and MRI data. The median number of months (and range) between MRI and CSF examinations was 1.4 months (range 0.04–11.8 months). The characteristics of the final sample of 226 cognitively healthy individuals are described in Table 1.

2.2 | Clinical examinations

The clinical examinations included extensive psychiatric, cognitive, psychological, and somatic assessments, and were performed at an outpatient clinic at the Sahlgrenska University Hospital in Gothenburg as described previously.[29] The CDR and the Mini-Mental State Examination (MMSE) were used to assess global cognitive status, as previously described.[29] The raters were not aware of results from MRI or CSF when rating the CDR.

2.3 | Analyses of CSF biomarkers

CSF Aβ42 concentration was measured using sandwich enzyme-linked immunosorbent assay (ELISA; INNOTEST β-amyloid$_{1\text{-}42}$), specifically constructed to measure Aβ starting at amino acid 1 and ending at amino acid 42.[31] CSF t-tau and p-tau (p-tau181) concentrations were measured using sandwich ELISA by INNOTEST (hTau-Ag and phospho-tau [181P]).[32,33] The Aβ42/Aβ40 ratio was measured using the V-PLEX Aβ Peptide Panel 1 (6E10) Kit (MesoScale Discovery).[34] CSF Ng concentration was measured using an in-house sandwich ELISA.[6] CSF NfL concentration was measured using the ELISA kit from UmanDiagnostics.[6] All assays were performed in a single batch. The standard clinical cut-off used to define Aβ42 pathology (Aβ-positives) was Aβ42 $\leq$ 530 pg/mL^3, with all other values being defined as clinically normal (Aβ-negatives).

2.4 | Apolipoprotein E genotyping

Genotyping to determine apolipoprotein E (*APOE*) ε4 allele carriership was performed using KASP technology (LGC, Genomics).[29] Those with at least an *APOE* ε4 allele were defined as ε4 carriers (i.e., individuals with the ε2/ε4, ε3/ε4, or ε4/ε4 genotype).

2.5 | MRI data acquisition and processing

The structural brain images were acquired at one site using a 3T MRI Philips Achieva scanner. A high-resolution sagittal 3D-T1 turbo field echo was used with the following scanning parameters: repetition time/echo time = 7.2/3.2 ms, field of view in mm = 256 × 256, matrix in mm = 250 × 250, flip angle = 9°, slice thickness = 1 mm. The FreeSurfer version 7.2.0[35] pipeline was used to estimate the total intracranial volume (ICV), cortical volumes, thicknesses, and areas as well as the volumes (in mm^3) of the hippocampus and amygdala.[30,36] The cerebral cortex was automatically delineated into 34 cortical regions of interest (ROIs) for each hemisphere.[37] We constructed a composite AD cortical thickness score (cortical AD signature score) including entorhinal, middle temporal, inferior temporal, and fusiform thicknesses,[38] corrected for the surface area of each region.

The TBF was automatically extracted from the warped gray matter (GM) segments by summing up the modulated GM voxel values within ROI masks using Statistical Parametric Mapping version 8 software (SPM8).[39] To simplify interpretation, we averaged the right and left hemispheres of the MRI volumes.[40] All MRI volumes were ICV-adjusted using the residual approach.[41] Quality control was carried out on MRI data according to previously described procedures,[42] and data management and processing were done through our database system, TheHiveDB.[30] Visual inspection was performed on image processing output to ensure correct segmentation.

2.6 | Statistical analysis

The analyses were based on data from cross-sectional examinations of the CSF biomarker levels and MRI measures. As a first stage, both CSF biomarkers and MRI measures were z transformed before fitting the

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional sources (e.g., PubMed). Studies of the association of cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) and neurodegeneration with magnetic resonance imaging (MRI) measures in cognitively healthy individuals have mainly focused on amyloid beta and tau in relation to cortical integrity and hippocampus volume in age-diverse samples. Studies including other CSF and MRI biomarkers of potential importance for AD, and studies performed in age-homogenous population-based samples, are lacking. Relevant references are appropriately cited.
2. **Interpretation**: Our findings support the hypothesis that AD-specific CSF biomarkers are related to total basal forebrain, hippocampus, and amygdala in cognitively healthy individuals, but contradict previous findings showing an association with cortical thickness.
3. **Future directions**: Associations of CSF biomarkers of AD and neurodegeneration with MRI measures need to be investigated in age-homogeneous population-based samples of cognitively healthy individuals followed over time.

TABLE 1 Sample characteristics in 226 cognitively healthy individuals.

Variables	Total ($n = 226$)	Aβ-positives ($n = 55$)	Aβ-negatives ($n = 171$)	*P* value
Sex (women), *n* (%)	116 (51.3)	25 (45.5)	91 (53.2)	0.4
APOE ε4 carrier, *n* (%)	78 (35.1)[a]	31 (57.4)	47 (28)	**0.0001**
Age (years), mean (SD)	70.9 (0.4)	70.9 (0.4)	70.9 (0.4)	0.7
MMSE, mean (SD)	29.3 (0.9)[b]	29.3 (0.9)	29.3 (0.9)	0.9
Education (years), mean (SD)	13.2 (3.9)	13.2 (3.7)	13.3 (4)	0.9
Aβ42 levels (pg/mL), mean (SD)	718.1 (225.8)	412 (85)	817 (159)	–
T-tau levels (pg/mL), mean (SD)	333.3 (137.8)	371 (184)	321 (117)	**0.02**
P-tau levels (pg/mL), mean (SD)	50.0 (17.8)	53.6 (22.6)	48.9 (53.6)	0.1
Ng levels (pg/mL), mean (SD)	207.8 (69.5)[c]	210 (75.6)	207 (67.7)	0.8
NfL levels (pg/mL), mean (SD)	886.9 (725.9)[d]	853 (437)	898 (796)	0.7
Hippocampus volume (mm^3), mean (SD)	3964.4 (302.7)	3929.1 (305)	3975.7 (302)	0.3
Amygdala volume (mm^3), mean (SD)	449.5 (189.3)	428.8 (218)	456.2 (179)	0.4
TBF volume (mm^3), mean (SD)	535.5 (52.9)	528.6 (47.5)	537.7 (54.5)	0.3
Cortical AD signature score (mm), mean (SD)	2.7 (0.1)	2.7 (0.1)	2.7 (0.1)	0.2

Notes: Missing data: $n^a = 4$, $n^b = 1$, $n^c = 1$, and $n^d = 1$. Age (years); age at lumbar puncture examination. Aβ-positives: pathological CSF Aβ42 (≤ 530 pg/mL), Aβ-negatives: normal CSF Aβ42 level (> 530 pg/mL). Cortical AD signature score includes entorhinal, middle temporal, inferior temporal, and fusiform.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; NfL, neurofilament light; Ng, neurogranin; p-tau, phosphorylated tau; SD, standard deviation; TBF, total basal forebrain; t-tau, total tau.

regression models for easy interpretation of the results in the same figure. The same models were then also applied on *z*-transformed values of the CSF biomarkers, but non-transformed values of the MRI measures. Sample characteristics are presented for the total sample and the subgroups Aβ-positives (individuals presenting clinically significant Aβ42 pathology) and Aβ-negatives (individuals with clinically normal Aβ42 levels). Statistical analyses were performed to compare sample characteristics between the two subgroups. An independent-sample *t* test was used to compare mean values of continuous variables (age in years, MMSE score, education in years, and levels of CSF biomarkers). Fisher exact test was used to compare the distribution of categorical variables (sex and *APOE ε4* status).

Linear regressions adjusted for sex were used to test the associations between CSF biomarkers and MRI measures, both in the total sample and after stratifying the sample based on Aβ42 pathology. A *P* value < 0.05 was considered significant. Both uncorrected *P* values and *P* values corrected for multiple testing based on false discovery rate were presented. Analyses were performed in RStudio 4.0.3 (R Foundation for Statistical Computing) using reference packages.[43]

3 | RESULTS

3.1 | Characteristics of the study population

As shown in Table 1, 51.3% were women, 32.2% were Aβ-positives, and 35.1% were *APOE ε4* carriers. The mean age was 70.9 years (standard deviation [SD] = 0.4), the mean years of education were 13.2 (SD = 3.9), and the mean MMSE score was 29.3 (SD = 0.9). The groups with Aβ-positives and Aβ-negatives differed in number of *APOE ε4* carriers and t-tau levels ($P = 0.0001$ and $P = 0.02$, respectively), but not in age, education, or MMSE. The raw data of the CSF variables in relation to the raw data of the MRI variables are visualized in the total sample and after stratification on Aβ42 pathology (Figures 1 and 2).

3.2 | Associations between CSF biomarkers and MRI measures

In the total sample ($n = 226$), higher t-tau levels were associated with smaller amygdala volume (beta = −0.15, standard error [SE] = 0.07, $P = 0.03$; Figure 3A, Figure S1 in supporting information, and Table 2), and lower Aβ42 levels were associated with smaller TBF volume (beta = 0.15, SE = 0.07, $P = 0.02$; Figure 3A, Figure S2 in supporting information, and Table 2). These results did not survive correction for multiple testing (Table 2) and the association between Aβ42 and TBF was not present when Aβ42 was replaced by the Aβ42/Aβ40 ratio (Table S1 in supporting information).

In individuals with Aβ42 pathology ($n = 55$), higher t-tau and p-tau levels were associated with smaller volumes of the hippocampus (beta = −0.33, SE = 0.1, $P = 0.001$ and beta = −0.33, SE = 0.1, $P = 0.003$; Figure 3B, Figure S3 in supporting information, and Table 2) and amygdala (beta = −0.34, SE = 0.11, $P = 0.005$ and beta = −0.31, SE = 0.12, $P = 0.01$; Figure 3B, Figure S1, and Table 2). The findings remained significant after correction for multiple testing (Table 2).

In individuals with normal Aβ42 levels (n = 171), higher t-tau, p-tau, and Ng levels were associated with larger TBF volumes (beta = 0.30,

SE = 0.09, P = 0.001, beta = 0.29, SE = 0.09, P = 0.001 and beta = 0.21, SE = 0.09, P = 0.008; Figure 3C, Figure S2, and Table 2). The findings remained significant after correction for multiple testing (Table 2), except that the relation with Ng only reached a trend toward significance (P = 0.054).

No associations were observed between the CSF biomarkers and the cortical AD signature score (Table 2, Figure 3, Figure S4 in supporting information) or between NfL levels and any of the MRI brain measures (Table 2). All analyses were repeated after adding education as a covariate, but the results did not change significantly (Table S2 in supporting information).

4 | DISCUSSION

In a population-based sample of cognitively healthy 70-year-olds, higher CSF t-tau levels were associated with smaller volume of the amygdala, and lower CSF Aβ42 levels were associated with smaller TBF volume. These associations did not, however, survive correction for multiple testing. Among individuals who had Aβ42 pathology, higher levels of CSF t-tau and p-tau were associated with smaller volumes of the hippocampus and amygdala, and among individuals with normal Aβ42 levels, higher CSF t-tau, p-tau, and Ng were associated with larger TBF volume. Most of these findings survived correction for multiple testing (corrected result for Ng vs. TBF only reached a trend toward significance). No associations were observed between the CSF biomarkers and the cortical AD signature score or between CSF NfL levels and any of the MRI brain measures.

The finding that higher t-tau levels were associated with smaller volume of the amygdala in the total sample did not survive correction for multiple testing and can therefore be considered in line with previous studies in cognitively healthy individuals.[17,24,44] The association we detected between lower Aβ42 levels and smaller volumes of TBF in the total sample could neither be seen in analyses in which Aβ42 was replaced by the Aβ42/Aβ40 ratio, nor be detected after correction for multiple testing. This contradicts findings in amyloid PET studies on cognitively healthy individuals.[27,28] The associations reported in previous studies were, however, restricted to individuals with high Aβ burden.

Our finding that associations between higher concentrations of t-tau, p-tau, and smaller volumes of AD-specific brain measures (i.e., hippocampus and amygdala) were observed among those with pathological Aβ42, but not among those with normal Aβ42, suggests that amyloid pathology is necessary, but not sufficient, for the early neurodegenerative process of AD, and is in line with the hypothesis by Jack et al.[5,45] This hypothesis states that the first sign of AD is pathological CSF Aβ42, occurring before clinical symptoms, and that brain atrophy does not occur until p-tau reaches abnormal levels.[5,46] Overall, our analyses of the total sample did not reveal any convincing associations, but the weak association between Aβ42 and TBF may, if not spurious, indicate that TBF is an earlier affected region than the hippocampus and amygdala (for which associations primarily were seen in those with Aβ42 pathology). This finding needs, however, to be validated externally. We have only identified one previous study in cognitively healthy individuals that performed analyses in individuals with and without Aβ42 pathology as separate groups,[17] but this study did not, in contradiction to ours, find any associations between t-tau and p-tau and hippocampus or amygdala volumes.

We found unexpected associations between higher t-tau, p-tau, and Ng levels and larger TBF volume among cognitively healthy individuals with normal levels of Aβ42. This finding is however somewhat in line with a previous study that reported unexpected associations between high CSF t-tau and Ng and lower ventricle volume in individuals with normal Aβ42 levels.[47] The authors suggested this association is possibly related to normal neuronal function or transmission. Another possible explanation might be alternative pathologies, such as transactive response DNA binding protein-43 (TDP-43), α-synuclein, and/or cerebrovascular pathologies, being involved. However, the group of Aβ-negatives included is heterogeneous (as can be seen by the huge standard deviations in Table 1) and the numbers with elevated levels of t-tau, p-tau, and Ng are relatively small in this population-based study compared to clinical samples. A probable explanation is therefore that our finding is coincidental and cannot be generalized to other cognitively healthy samples. A previous study has reported enlarged septal

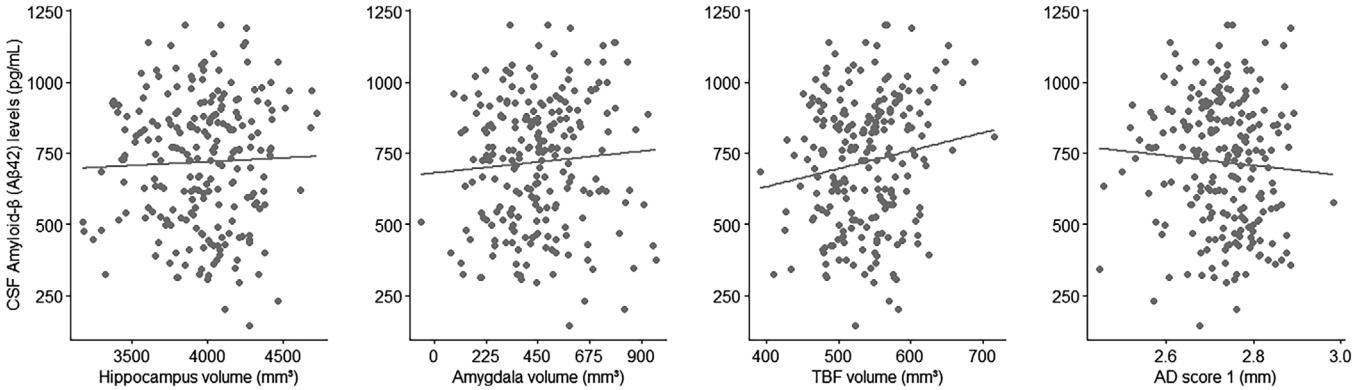

FIGURE 1 Relations between CSF Aβ42 and MRI measures in the total sample. Gray lines are the correlation lines showing the trends. Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; TBF, total basal forebrain.

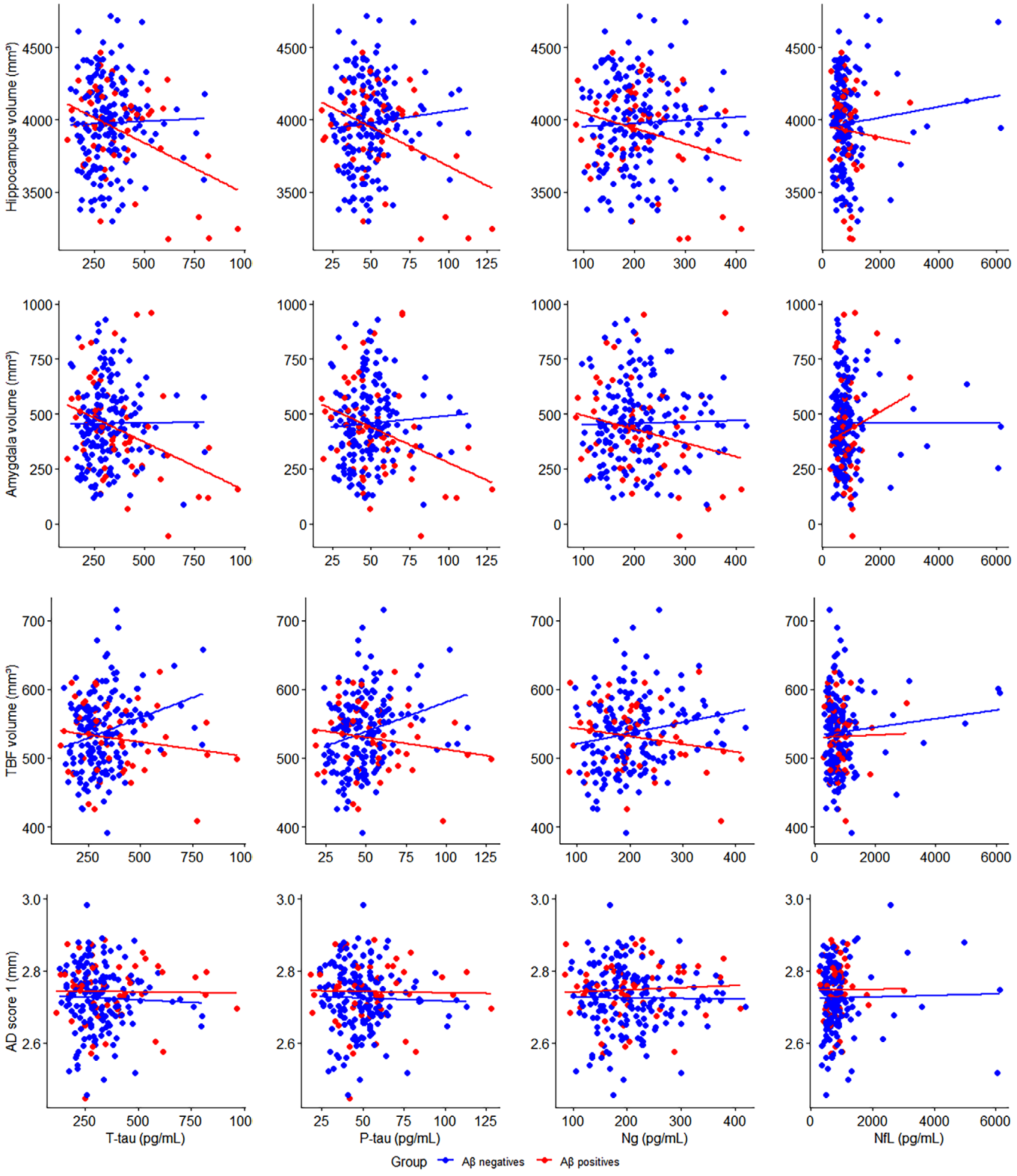

FIGURE 2 Relations between CSF biomarkers and MRI measures after stratification on Aβ42 pathology. Red dots = Aβ-positives: ≤ 530 pg/mL. Blue dots = Aβ-negatives: > 530 pg/mL. Red lines are the correlation lines showing the trends for Aβ-positives and blue lines are the correlation lines showing the trends for Aβ-negatives. Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; TBF, total basal forebrain.

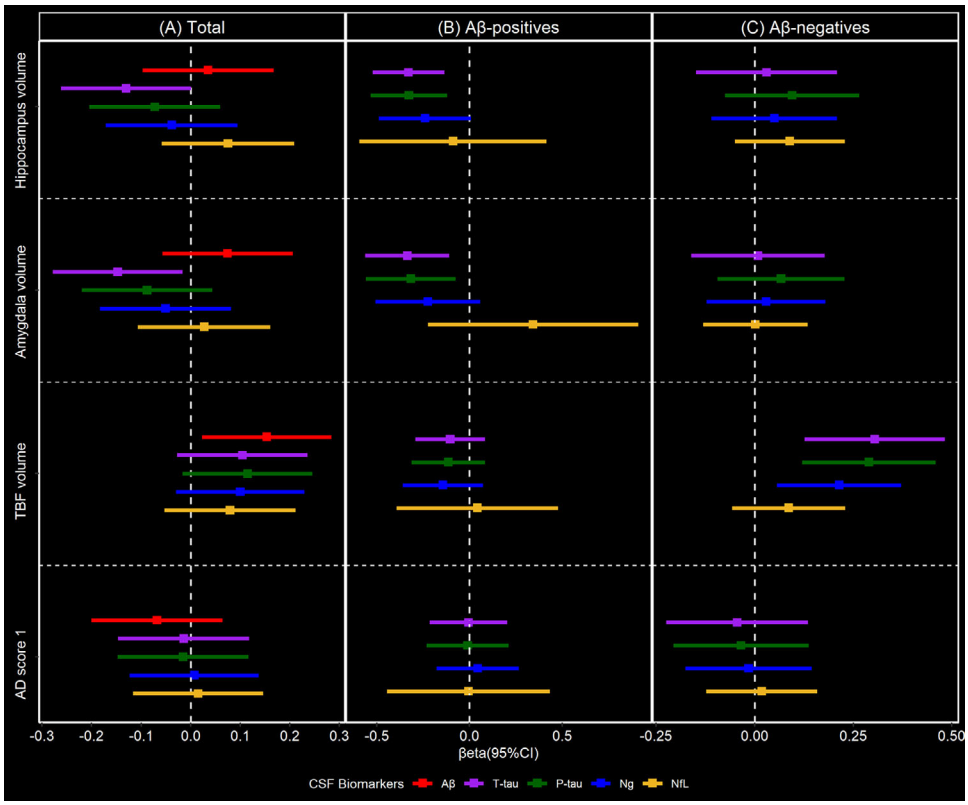

FIGURE 3 Forest plot of the associations between CSF biomarkers and MRI measures in the total sample (A), and after stratification on Aβ42 pathology, (B) Aβ-positives: ≤ 530 pg/mL, and (C) Aβ-negatives: > 530 pg/mL. Aβ, amyloid beta; AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; TBF, total basal forebrain.

nuclei of the basal forebrain in cognitively normal individuals who later develop AD.[48] In support of this, a longitudinal study of asymptomatic AD patients reported that both cortical and subcortical areas undergo significant neuronal hypertrophy as a reaction to early AD pathology.[49] One could possibly speculate this is due to hypertrophic compensatory mechanisms or an inflammatory response (generating neuronal or glial swelling),[50] as a very early reaction to the presence of AD pathology. However, the associations seen in our study were among individuals who had normal levels of Aβ42, and thus may not be considered at risk of AD. Moreover, it is a bit puzzling that we found an association with t-tau but not with NfL, as both are biomarkers of neurodegeneration.

We did not find associations between NfL and any of the MRI measures, which contradicts previous studies reporting associations between CSF NfL and a temporoparietal region including the hippocampus and amygdala,[18] or cortical thickness,[17] in cognitively unimpaired adults. Our lack of associations may be due to few people with elevated NfL or low variability of this biomarker in our study. Further, we did not find associations between any of the CSF biomarkers and the cortical AD signature score, but previous studies on cognitively healthy individuals reported associations between Aβ, p-tau, Ng, or NfL and a thinner cortex of the regions included in the AD signature score.[14,17,24] The lack of association in our study might be due to an early stage of disease. Comparisons to previous results are however somewhat difficult to interpret due to differences in study design (i.e., their sample was smaller and not population based, and the age range was wide).

Among the strengths of this study are the representative population-based sample recruited by prespecified birth dates, the comprehensive examinations, and the relatively large sample of cognitively healthy individuals with both CSF and MRI measures. Further, the study design including an age-homogeneous sample is a strength because previous studies have shown that AD-related brain pathology (i.e., hippocampal atrophy) differs in a non-linear way among age groups of older individuals.[51]

However, there are also some limitations. First, the study is cross-sectional and we cannot draw any conclusions regarding the direction of the associations. Second, only one third of the participants consented to LP, and almost one quarter of those who accepted were excluded due to contraindications, mainly due to the use of anticoagulation therapy, indicating the challenges in conducting population-based CSF studies. However, when investigating a number of factors,[3] CSF participants only differed from those who declined LP by more often being men. Third, in an age-homogeneous and cognitively healthy sample the variations in CSF biomarker and MRI measure values are small and the power to find associations is limited, despite the relatively large sample size.

In conclusion, in this population-based study, we found associations in the expected direction (i.e., higher t-tau and p-tau were associated with lower MRI marker volume) in individuals with Aβ42 pathology.

TABLE 2 Linear regression associations between CSF biomarker levels and MRI measures in the total sample and stratified on Aβ42 pathology, adjusted for sex.

MRI measure	CSF biomarker level	Beta	Lower CI	Upper CI	SE	*P* value	FDR
Total (*n* = 226)							
Hippocampal volume	Aβ42	0.0352	−0.0970	0.1675	0.0671	0.6	0.8
	T-tau	−0.1305	−0.2618	0.0008	0.0666	0.05	0.3
	P-tau	−0.0726	−0.2044	0.0592	0.0669	0.3	0.5
	Ng	−0.0383	−0.1713	0.0948	0.0675	0.6	0.8
	NfL	0.0909	−0.0420	0.2239	0.0675	0.2	0.5
Amygdala volume	Aβ42	0.0745	−0.0573	0.2063	0.0669	0.3	0.5
	T-tau	−0.1472	−0.2780	−0.0163	0.0664	**0.03**	0.3
	P-tau	−0.0880	−0.2195	0.0435	0.0667	0.2	0.5
	Ng	−0.0508	−0.1832	0.0816	0.0672	0.5	0.7
	NfL	0.0355	−0.0973	0.1683	0.0674	0.6	0.9
TBF volume	Aβ42	0.1536	0.0231	0.2841	0.0662	**0.02**	0.3
	T-tau	0.1043	−0.0271	0.2357	0.0667	0.1	0.4
	P-tau	0.1147	−0.0164	0.2457	0.0665	0.1	0.4
	Ng	0.1001	−0.0294	0.2296	0.0657	0.1	0.4
	NfL	0.0440	−0.0881	0.1761	0.0670	0.5	0.5
AD score 1	Aβ42	−0.0680	−0.2000	0.0639	0.0670	0.3	0.5
	T-tau	−0.0141	−0.1465	0.1183	0.0672	0.8	0.9
	Ng	−0.0153	−0.1475	0.1168	0.0671	0.8	0.9
	P-tau	0.0072	−0.1228	0.1373	0.0660	0.9	0.9
	NfL	0.0046	−0.1259	0.1351	0.0662	0.9	0.9
Aβ-positives (*n* = 55)							
MRI measure	**CSF biomarker level**	**Beta**	**Lower CI**	**Upper CI**	**SE**	***P* value**	**FDR**
Hippocampal volume	T-tau	−0.3292	−0.5226	−0.1359	0.0964	**0.001**	**0.02**
	P-tau	−0.3269	−0.5331	−0.1206	0.1028	**0.003**	**0.02**
	Ng	−0.2399	−0.4882	0.0083	0.1237	0.06	0.2
	NfL	−0.1289	−0.8612	0.6033	0.3646	0.7	1.0
Amygdala volume	T-tau	−0.3355	−0.5620	−0.1091	0.1128	**0.005**	**0.02**
	P-tau	−0.3169	−0.5594	−0.0745	0.1208	**0.01**	**0.045**
	Ng	−0.2248	−0.5084	0.0588	0.1413	0.1	0.3
	NfL	0.4979	−0.3252	1.3210	0.4098	0.2	0.4
TBF volume	T-tau	−0.1042	−0.2923	0.0839	0.0937	0.3	0.4
	P-tau	−0.1141	−0.3121	0.0838	0.0986	0.3	0.4
	Ng	−0.1435	−0.3602	0.0732	0.1079	0.2	0.4
	NfL	0.0609	−0.5716	0.6934	0.3149	0.8	1.0
AD score 1	T-tau	−0.0061	−0.2153	0.2031	0.1042	1	1.0
	P-tau	−0.0103	−0.2306	0.2101	0.1098	0.9	1.0
	Ng	0.0440	−0.1774	0.2653	0.1103	0.7	1.0
	NfL	−0.0083	−0.6460	0.6293	0.3175	1	1.0

(Continues)

TABLE 2 (Continued)

Aβ-negatives ($n = 171$)							
MRI measure	CSF biomarker level	Beta	Lower CI	Upper CI	SE	*P* value	FDR
Hippocampal volume	T-tau	0.0302	−0.1486	0.2089	0.0905	0.7	1.0
	P-tau	0.0949	−0.0751	0.2649	0.0861	0.3	0.7
	Ng	0.0497	−0.1094	0.2088	0.0806	0.5	1.0
	NfL	0.0981	−0.0375	0.2338	0.0687	0.2	0.7
Amygdala volume	T-tau	0.0085	−0.1607	0.1778	0.0857	0.9	1.0
	P-tau	0.0669	−0.0943	0.2281	0.0817	0.4	1.0
	Ng	0.0291	−0.1217	0.1798	0.0763	0.7	1.0
	NfL	0.0177	−0.1111	0.1464	0.0652	0.8	1.0
TBF volume	T-tau	0.3046	0.1270	0.4822	0.0899	**0.001**	**0.007**
	P-tau	0.2898	0.1203	0.4593	0.0859	**0.001**	**0.007**
	Ng	0.2141	0.0563	0.3719	0.0799	**0.01**	**0.04**
	NfL	0.0458	−0.0941	0.1858	0.0709	0.5	0.7
AD score 1	T-tau	−0.0446	−0.2241	0.1349	0.0909	0.6	1.0
	P-tau	−0.0347	−0.2060	0.1367	0.0868	0.7	1.0
	Ng	−0.0153	−0.1753	0.1448	0.0811	0.9	1.0
	NfL	0.0085	−0.1286	0.1457	0.0695	0.9	1.0

Notes: Aβ-negatives: normal CSF Aβ42 level (> 530 pg/mL), Aβ-positives: pathological CSF Aβ42 (≤ 530 pg/mL). AD score 1: cortical AD signature score including entorhinal, middle temporal, inferior temporal, and fusiform. FDR: PFDR with alpha of 0.05.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; FDR, false discovery rate; MRI, magnetic resonance imaging; NfL, neurofilament light; Ng, neurogranin; p-tau, phosphorylated tau; SE, standard error; TBF, total basal forebrain; t-tau, total tau.

These associations indicate that AD-specific CSF biomarkers may be related to hippocampus, and amygdala, but not to cortical thickness, among cognitively healthy 70-year-olds from the general population. Among individuals with normal Aβ42 levels, we found unexpected associations of higher tau and Ng with larger TBF volume, which might be related to normal neuronal function or could possibly be explained as a coincidental finding in our specific sample.

ACKNOWLEDGMENTS

The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALF 716681, ALF-965812); the Swedish Research Council (2012-5041, 2015-02830, 2019-01096, 2013-8717, 2017-00639, 2022-00882); Swedish Research Council for Health, Working Life and Welfare (2013-1202>, 2018-00471, AGECAP 2013-2300, 2013-2496); Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Hjärnfonden, Alzheimerfonden, Eivind och Elsa K:son Sylvans stiftelse. KB was supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-930351, #AF-939721 and #AF-968270), Hjärnfonden, Sweden (#FO2017-0243 and #ALZ2022-0006), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986 and #ALFGBG-965240), the European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), the National Institute of Health, USA, (grant #1R01AG068398-01), and the Alzheimer's Association 2021 Zenith Award (ZEN-21-848495). SK was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-965923, ALFGBG-81392, ALF GBG-771071), The Alzheimerfonden (AF-842471, AF-737641, AF-929959, AF-939825), The Swedish Research Council (2019-02075), Psykiatriska Forskningsfonden, Stiftelsen Demensfonden, Stiftelsen Hjalmar Svenssons Forskningsfond, Stiftelsen Wilhelm och Martina Lundgrens vetenskapsfond. HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care

Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL (UKDRI-1003).

CONFLICT OF INTEREST STATEMENT

KB has served as a consultant, on advisory boards, or data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). SK has served on scientific advisory boards and/or as a consultant for Geras Solutions, Optoceutics, and Biogen, unrelated to the present study. The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

ETHICAL APPROVAL AND INFORMED CONSENT

This study was approved by the Regional Ethical Review Board in Gothenburg. Informed consent was obtained from all participants and or their relatives if they were not able to provide their own consent.

REFERENCES

1. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2015;11(3):332-384.
2. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med*. 2018;284(6):643-663.
3. Kern S, Zetterberg H, Kern J, et al. Prevalence of preclinical Alzheimer disease: comparison of current classification systems. *Neurology*. 2018;90(19):e1682-e1691.
4. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.
5. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128.
6. Skoog I, Kern S, Najar J, et al. A Non-APOE polygenic risk score for Alzheimer's disease is associated with cerebrospinal fluid neurofilament light in a representative sample of cognitively unimpaired 70-year olds. *J Gerontol A Biol Sci Med Sci*. 2021;76(6):983-990.
7. Desikan RS, Mcevoy LK, Thompson WK, et al. Amyloid-β associated volume loss occurs only in the presence of phospho-tau. *Ann Neurol*. 2011;70(4):657-661.
8. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex*. 2009;19(3):497-510.
9. Lehericy S, Baulac M, Chiras J. Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. *AJNR Am J Neuroradiol*. 1994;15(5):929-937.
10. Ballinger EC, Ananth M, Talmage DA, Role LW. Basal forebrain cholinergic circuits and signaling in cognition and cognitive decline. *Neuron*. 2016;91(6):1199-1218.
11. Harrison TM, Du R, Klencklen G, Baker SL, Jagust WJ. Distinct effects of beta-amyloid and tau on cortical thickness in cognitively healthy older adults. *Alzheimers Dement*. 2021;17(7):1085-1096.
12. Fotenos AF, Mintun MA, Snyder AZ, Morris JC, Buckner RL. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. *Arch Neurol*. 2008;65(1):113-120.
13. Bourgeat P, Chételat G, Villemagne VL, et al. Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. *Neurology*. 2010;74(2):121-127.
14. Ekblad LL, Visser PJ, Tijms BM. Proteomic correlates of cortical thickness in cognitively normal individuals with normal and abnormal cerebrospinal fluid beta-amyloid(1-42). *Neurobiol Aging*. 2021;107:42-52.
15. Johnson SC, Christian BT, Okonkwo OC, et al. Amyloid burden and neural function in people at risk for Alzheimer's Disease. *Neurobiol Aging*. 2014;35(3):576-584.
16. Salvadó G, Shekari M, Falcon C, et al. Brain alterations in the early Alzheimer's continuum with amyloid-β, tau, glial and neurodegeneration CSF markers. *Brain Commun*. 2022;4(3):fcac134.
17. Pereira JB, Westman E, Hansson O. Association between cerebrospinal fluid and plasma neurodegeneration biomarkers with brain atrophy in Alzheimer's disease. *Neurobiol Aging*. 2017;58:14-29.
18. Saloner R, Fonseca C, Paolillo EW, et al. Combined effects of synaptic and axonal integrity on longitudinal gray matter atrophy in cognitively unimpaired adults. *Neurology*. 2022;99(20):e2285-e2293.
19. Chételat G, Villemagne VL, Pike KE, et al. Larger temporal volume in elderly with high versus low beta-amyloid deposition. *Brain: J Neurol*. 2010;133(11):3349-3358.
20. Doré V, Villemagne VL, Bourgeat P, et al. Cross-sectional and longitudinal analysis of the relationship between Aβ deposition, cortical thickness, and memory in cognitively unimpaired individuals and in alzheimer disease. *JAMA Neurol*. 2013;70(7):903-911.
21. Arenaza-Urquijo EM, Molinuevo J-L, Sala-Llonch R, et al. Cognitive reserve proxies relate to gray matter loss in cognitively healthy elderly with abnormal cerebrospinal fluid amyloid-β levels. *J Alzheimers Dis*. 2013;35(4):715-726.
22. Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain*. 2009;132(Pt 5):1310-1323.
23. Stricker NH, Dodge HH, Dowling NM, Han SD, Erosheva EA, Jagust WJ. CSF biomarker associations with change in hippocampal volume and precuneus thickness: implications for the Alzheimer's pathological cascade. *Brain Imaging Behav*. 2012;6(4):599-609.
24. Pettigrew C, Soldan A, Sloane K, et al. Progressive medial temporal lobe atrophy during preclinical Alzheimer's disease. *Neuroimage Clin*. 2017;16:439-446.
25. Llibre-Guerra JJ, Li Y, Schindler SE, et al. Association of longitudinal changes in cerebrospinal fluid total tau and phosphorylated tau 181 and brain atrophy with disease progression in patients with Alzheimer disease. *JAMA Netw Open*. 2019;2(12):e1917126.
26. Storandt M, Mintun MA, Head D, Morris JC. Cognitive decline and brain volume loss as signatures of cerebral amyloid-beta peptide deposition identified with Pittsburgh compound B: cognitive decline associated with Abeta deposition. *Arch Neurol*. 2009;66(12):1476-1481.

27. Grothe MJ, Ewers M, Krause B, Heinsen H, Teipel SJ, Alzheimer's Disease Neuroimaging Initiative. Basal forebrain atrophy and cortical amyloid deposition in nondemented elderly subjects. *Alzheimers Dement*. 2014;10(5):S344-S353.
28. Kerbler GM, Fripp J, Rowe CC, et al. Basal forebrain atrophy correlates with amyloid β burden in Alzheimer's disease. *Neuroimage Clin*. 2015;7:105-113.
29. Rydberg Sterner T, Ahlner F, Blennow K, et al. The Gothenburg H70 Birth cohort study 2014-16: design, methods and study population. *Eur J Epidemiol*. 2019;34(2):191-209.
30. Muehlboeck JS, Westman E, Simmons A. TheHiveDB image data management and analysis framework. *Front Neuroinform*. 2014;7:49.
31. Andreasen N, Hesse C, Davidsson P, et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch Neurol*. 1999;56(6):673-680.
32. Blennow K, Wallin A, Ågren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Mol Chem Neuropathol*. 1995;26(3):231-245.
33. Vanmechelen E, Vanderstichele H, Davidsson P, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neurosci Lett*. 2000;285(1):49-52.
34. Steen Jensen C, Portelius E, Siersma V, Høgh P, et al. Cerebrospinal fluid amyloid beta and tau concentrations are not modulated by 16 weeks of moderate- to high-intensity physical exercise in patients with Alzheimer disease. *Dement Geriatr Cogn Disord*. 2016;42(3-4):146-158.
35. FreeSurfer, Accessed September 2021, 2021. https://surfer.nmr.mgh.harvard.edu/
36. Lindberg O, Kern S, Skoog J, et al. Effects of amyloid pathology and the APOE epsilon4 allele on the association between cerebrospinal fluid Abeta38 and Abeta40 and brain morphology in cognitively normal 70-years-olds. *Neurobiol Aging*. 2021;101:1-12.
37. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980.
38. Jack CR, Wiste HJ, Weigand SD, et al. Different definitions of neurodegeneration produce similar amyloid/neurodegeneration biomarker group findings. *Brain*. 2015;138(Pt 12):3747-3759.
39. Kilimann I, Grothe M, Heinsen H, et al. Subregional basal forebrain atrophy in Alzheimer's disease: a multicenter study. *J Alzheimers Dis*. 2014;40(3):687-700.
40. Westman E, Muehlboeck J-S, Simmons A. Combining MRI and CSF measures for classification of Alzheimer's disease and prediction of mild cognitive impairment conversion. *Neuroimage*. 2012;62(1):229-238.
41. Voevodskaya O, Simmons A, Nordenskjöld R, et al. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. *Front Aging Neurosci*. 2014;6:264.
42. Simmons A, Westman E, Muehlboeck S, et al. The AddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease: experience from the first 24 months. *Int J Geriatr Psychiatry*. 2011;26(1):75-82.
43. R Core Team. *R: A language and environment for statistical computing. R Foundation for Statistical Computing*. 2020. http://www.r-project.org/index.html
44. Tosun D, Schuff N, Truran-Sacrey D, et al. Relations between brain tissue loss, CSF biomarkers, and the ApoE genetic profile: a longitudinal MRI study. *Neurobiol Aging*. 2010;31(8):1340-1354.
45. Kester MI, Teunissen CE, Crimmins DL, et al. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer disease. *JAMA Neurol*. 2015;72(11):1275-1280.
46. Buchhave P. Cerebrospinal fluid levels of beta-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch Gen Psychiatry*. 2012;69(1):98-106.
47. Mattsson N, Insel PS, Palmqvist S, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. *EMBO Mol Med*. 2016;8(10):1184-1196.
48. Butler T, Harvey P, Deshpande A, et al. Basal forebrain septal nuclei are enlarged in healthy subjects prior to the development of Alzheimer's disease. *Neurobiol Aging*. 2018;65:201-205.
49. Iacono D, O'brien R, Resnick SM, et al. Neuronal hypertrophy in asymptomatic Alzheimer disease. *J Neuropathol Exp Neurol*. 2008;67(6):578-589.
50. Femminella GD, Dani M, Wood M, et al. Microglial activation in early Alzheimer trajectory is associated with higher gray matter volume. *Neurology*. 2019;92(12):e1331-e1343.
51. Zhang Yi, Qiu C, Lindberg O, et al. Acceleration of hippocampal atrophy in a non-demented elderly population: the SNAC-K study. *Int Psychogeriatr*. 2010;22(1):14-25.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Seidu NM, Kern S, Sacuiu S, et al. Association of CSF biomarkers with MRI brain changes in Alzheimer's disease. *Alzheimer's Dement*. 2024;16:e12556. https://doi.org/10.1002/dad2.12556