Neurobiology of Aging 101 (2021) 1–12

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Effects of amyloid pathology and the *APOE* ε4 allele on the association between cerebrospinal fluid Aβ38 and Aβ40 and brain morphology in cognitively normal 70-years-olds

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ARTICLE INFO

Article history:
Received 9 June 2020
Received in revised form 26 October 2020
Accepted 29 October 2020

Keywords:
Amyloid-beta-38
Amyloid-beta-40
Structural-magnetic-resonance-imaging
Diffusion-tensor-imaging
Cognitively normal

ABSTRACT

The association between cerebrospinal fluid (CSF) amyloid beta (Aβ) Aβ38 or Aβ40 and brain grey- and white matter integrity is poorly understood. We studied this in 213 cognitively normal 70-year-olds, and in subgroups defined by presence/absence of the APOE ε4 allele and Aβ pathology: Aβ−/APOE−, Aβ+/APOE−, Aβ−/APOE+ and Aβ+/APOE+. CSF Aβ was quantified using ELISA and genotyping for *APOE* was performed. Low CSF Aβ42 defined Aβ plaque pathology. Brain volumes were assessed using Freesurfer-5.3, and white matter integrity using tract-based statistics in FSL. Aβ38 and Aβ40 were positively correlated with cortical thickness, some subcortical volumes and white matter integrity in the total sample, and in 3 of the subgroups: Aβ−/APOE−, Aβ+/APOE− and Aβ−/APOE+. In Aβ+/APOE+ subjects, higher Aβ38 and Aβ40 were linked to reduced cortical thickness and subcortical volumes. We hypothesize that production of all Aβ species decrease in brain regions with atrophy. In Aβ+/APOE+, Aβ-dysregulation may be linked to cortical atrophy in which high Aβ levels is causing pathological changes in the gray matter of the brain.

1. Introduction

The pathological accumulation of amyloid beta (Aβ) is believed to be caused by an imbalance between the production and clearance of the Aβ peptide in the brain (Hardy and Selkoe, 2002). Validated biomarkers for Aβ plaque pathology (Aβ pathology) consist of low levels of Aβ42 in cerebrospinal fluid (CSF) or retention of an amyloid tracer in the brain on positron emission tomography (PET) (Palmqvist et al., 2015) (Blennow and Zetterberg, 2018). Some studies suggest that the ratio CSF Aβ42/Aβ40 may improve the diagnostic accuracy of Aβ pathology (Janelidze et al., 2016). An increased processing of the amyloid precursor protein (APP) leading to increased Aβ production is suggested to be the predominant cause of the autosomal variant of AD (Moore et al., 2015), while both dysfunctional clearance (Mawuenyega et al., 2010) and increased Aβ production may cause the sporadic form of AD (Mattsson et al., 2016). The *APOE* ε4 allele is a genetic risk factor for late-onset AD (Morris et al., 2010). It has been shown that the main cause of Aβ pathology in people with the *APOE* ε4 allele (*APOE* ε4 allele-positive subjects) is a reduced capacity for Aβ-clearance

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0197-4580/
https://doi.org/10.1016/j.neurobiolaging.2020.10.033

(Castellano et al., 2011). Some authors suggest that CSF levels of Aβ38 and Aβ40 may be surrogate markers for APP-processing (Mattsson et al., 2016). High levels of Aβ38 and Aβ40 could thus potentially be indicators of overproduction of all Aβ species. Consistent with this hypothesis, one study showed that high levels of CSF Aβ38 and Aβ40 predicted Aβ fibrils (measured by 18F-flutemetamol PET) in the brain in a large cohort of normal and mildly cognitively impaired individuals (Mattsson et al., 2016). This association was stronger in *APOE* ε4-negative than in *APOE* ε4-positive individuals, potentially indicating that increased Aβ production is more strongly associated with Aβ-pathology in *APOE ε4*-negative than in *APOE ε4*-positive individuals. Further evidence that Aβ overproduction may cause Aβ pathology was found in a longitudinal study that showed that high CSF Aβ38 and Aβ40 levels predicted future decline in CSF Aβ42 levels (Tijms et al., 2018). High CSF Aβ38 and Aβ40 may thus be a sign of Aβ dysregulation, which may occur as long as 1–2 decades before onset of AD dementia (Bateman et al., 2012; Jack et al., 2013; Jansen et al., 2015; Villemagne et al., 2013). Low levels of CSF Aβ40 have been associated with the presence of other pathologies, such as cerebral amyloid angiopathy (CAA) (Chen et al., 2018), white matter lesions (Selnes et al., 2010) or subcortical injury (van Westen et al., 2016) (Janelidze et al., 2016). Moreover, low levels of CSF Aβ38 (Heywood et al., 2018) and low levels CSF of Aβ38 and Aβ40 (Gabelle et al., 2011) have been found in patients with frontotemporal dementia. In contrast, one animal study on the Caribbean vervet monkey (*Chlorocebus aethiops sabaeus*) found that high CSF Aβ40 levels were positively correlated with cortical thickness, hippocampal volume, white matter integrity in the corpus callosal area and total cortical surface area in the brain (Chen et al., 2018). Interestingly, this study found that low CSF Aβ40 was more strongly associated with cortical and subcortical volumes than other validated biomarkers for neurodegeneration such as total tau (Blennow and Zetterberg, 2015, 2018). Chen et al. notes that low levels of CSF Aβ40 is linked to vascular amyloid deposits in the brain (Verbeek et al., 2009), which may be associated with cortical thinning in the brain (Fotiadis et al., 2016). While the studies discussed above suggest that high CSF Aβ38 and Aβ40 levels may be predictors of Aβ-pathology, Aβ pathology itself has been shown to be an inconsistent predictor of structural gray and white matter brain changes in cognitively normal elderly subjects. Some studies report weak or no relationships (Steininger et al., 2014; Whitwell et al., 2013), others have found regional volume loss (Arenaza-Urquijo et al., 2013; Becker et al., 2011; Fagan et al., 2009; Storandt et al., 2009), while some studies report increased cortical thickness (Chetelat et al., 2010; Johnson et al., 2014) in individuals with Aβ-pathology. In an interesting study by Rahayel et al., subcortical amyloid load was found to be related to changes in cortical morphology in cognitively normal individuals (Rahayel et al., 2019).

The association between Aβ pathology and white matter integrity measured by fractional anisotropy (FA) and mean diffusivity (MD) on diffusion tensor imaging (DTI) has also been found to be inconsistent. Decreased FA (the directional coherence in water diffusion) and increased MD (the mean water diffusion) has been associated with decreased integrity of white matter (Le Bihan et al., 2001). One study found increased FA and decreased MD in subjects with high amyloid burden in the brain (Racine et al., 2014). Another large population-based study found that Aβ pathology was only associated with changes in FA and MD when it coexisted with gray matter atrophy (Kantarci et al., 2014).

CSF Aβ38 and Aβ40 levels are thus ambiguous biomarkers that may be elevated in the preclinical phase of AD but decreased in several other neurodegenerative diseases. Further, the studies discussed above indicate that the effect of high levels of Aβ is influenced by *APOE ε4* status. In this study we aim to investigate the association between CSF Aβ38 and Aβ40 levels and brain grey- and white matter in 213 cognitively normal 70 year olds. To further investigate this association in relation to 2 of the most well known risk factors for AD (the *APOE ε4* allele and Aβ42-pathology) we also performed the analyses in 4 subgroups: 1) participants without the *APOE* ε4 allele and without Aβ pathology (APOE−/Aβ−), 2) participants without the *APOE* ε4 allele with Aβ pathology (APOE−/Aβ+), 3) participants with the *APOE* ε4 allele and without Aβ pathology (APOE+/Aβ−) and 4) participants with the *APOE* ε4 allele and with Aβ pathology (APOE+/Aβ+).

2. Methods

2.1. Participants

The sample was included from the 2014–2016 examinations of the H70 Gothenburg Birth Cohort Studies in Gothenburg, Sweden (Rydberg Sterner et al., 2019). The sample was obtained from the Swedish Population Registry and included both persons living in private households and in residential care. Every 70-year-old in Gothenburg, Sweden, born during 1944 on prespecified birthdates was invited to the examination in 2014–2016, and 1203 participated (response rate 72.2%). Of these, 430 (35.8%) consented to a lumbar puncture. Contraindications (anticoagulant therapy, immune modulated therapy, cancer therapy) were present in 108, and CSF volume was insufficient for 4 participants, leaving 318 individuals (Kern et al., 2018). Both CSF and magnetic resonance imaging (MRI) were available for 299 participants. After strict post-processing quality control, 41 images were excluded from the analysis due to segmentation errors (n = 29), processing errors (n = 1), large infarcts (n = 8), large movements (n = 2) and the presence of a tumor (n = 1), leaving 258 participants. For the purpose of this study, we only included participants without cognitive problems defined as a clinical dementia rating (CDR) of 0 (Hughes et al., 1982). The final sample thus included 213 participants with CDR = 0.

2.2. Cerebrospinal fluid sampling and biomarker analyses

Lumbar punctures (LP) to collect CSF samples were performed in the L3/L4 or L4/L5 inter-space in the morning (Bjerke et al., 2016). All samples were collected and analyzed using identical procedure to avoid batch effects. The first 10 mL of CSF were collected in a polypropylene tube and immediately transported to the laboratory for centrifugation at 1800 g in 20 °C for 10 minutes. The supernatant was gently mixed to avoid possible gradient effects, aliquoted in polypropylene tubes and stored at −70 °C (Bjerke et al., 2016; Hoglund et al., 2017; Kern et al., 2018).

CSF concentrations of total tau and tau phosphorylated at threonine 181 (P-tau) were measured using a sandwich enzyme-linked immunosorbent-assay (ELISA) (INNOTEST htau Ag and PHOSPHO_TAU (181P), Fujirebio, Ghent, Belgium) (Blennow et al., 1995; Vanmechelen et al., 2000). CSF Aβ42 was measured using a sandwich ELISA (INNOTEST β-amyloid$_{1-42}$, Fujirebio, Ghent, Belgium), specifically constructed to measure Aβ starting at amino acid 1 and ending at amino acid 42 (Andreasen et al., 1999). For the Aβ42/Aβ40 ratio, Aβ38 and Aβ40 the V-PLEX Aβ Peptide Panel 1 (6E10) Kit (Meso Scale Discovery, Rockville, MD) was used (Steen Jensen et al., 2016). All assays are included in the panel of clinical routine analyses at the Mölndal Clinical Neurochemistry Laboratory. Analytical runs had to pass quality control criteria for the calibrators and internal quality control samples had to be approved. Aβ pathology was defined as CSF Aβ42 levels ≤530 pg/mL (Hansson et al., 2006) (Hoglund et al., 2017; Kern et al., 2018).

2.3. Neuropsychology

Neuropsychological examination was conducted by research staff members, all trained by a psychologist, with a total duration of

approximately one hour. The cognitive test battery was designed to cover a broad range of different cognitive abilities (see supplementary material).

2.4. Magnetic resonance imaging

2.4.1. MRI acquisition

MRI data was collected at a single site using one camera, a 3.0 T Philips Achieva system (Philips Medical Systems).

The MRI protocol consisted of a T1 3D 1 mm isotropic acquisition for structural changes with a repetition time = 7.2 milli seconds (ms), echo time = 3.2 ms. Field of view in mm = 256*256 mm and a flip angle of 9°.

A single shot SS SE-EPI sequence was used to acquire diffusion tensor images. Images were acquired with axial slices of 2*2*3 mm resolution, encoded with 1 b-value shell: 800k s/mm^2, along with 32 directions and 1 b = 0 image. Other acquisition parameters were: TE = 83 ms, TR = 7340 ms and FOV = 224 × 224 mm^2, flip angle = 90°, Several other sequences were acquired (Rydberg Sterner et al., 2019) but these were not used in the study.

2.4.2. MRI analysis

Cortical reconstruction and volumetric segmentation of subcortical volumes were performed on the T1 3D image using Freesurfer 5.3 image analysis pipeline, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications, which are listed at https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation. Briefly, the whole-brain T1-weighted images underwent a correction for intensity homogeneity, skull striping, and segmentation into GM and white matter (WM). Cortical thickness was measured as the distance from the gray/white matter boundary to the corresponding pial surface. Subcortical segmentation and assessment of intracranial volume was also performed in Freesurfer. Reconstructed data sets were visually inspected for accuracy, and segmentation errors were corrected. Quality control was carried out on all MRI data according to previous described procedure (Simmons et al., 2011), and data management and processing were done through our database system (Muehlboeck et al., 2014). Diffusion-weighted images were analyzed using the FMRIB's Diffusion Toolbox from FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) (Behrens et al., 2007). First, the data was corrected for distortions caused by eddy currents and head motion using the b0 non-diffusion data as a reference volume (Andersson and Skare, 2002). The resulting images were skull-striped and a diffusion tensor model was fitted at each voxel to determine the preferred diffusion direction as the principal eigenvector of the eigenvalue decomposition (Pierpaoli and Basser, 1996; Song et al., 2002). To provide information on the microstructural organization of the white matter, for each voxel the fractional anisotropy (FA) and mean diffusivity (MD) maps were computed (Beaulieu and Allen, 1994). The FA maps were transformed into MNI space using the tract-based spatial statistics tool. After normalization, FA images were resampled and subsequently merged into a single file to create a mean FA image for all subjects, which was then used to create a mean FA 'skeleton'. The threshold of the skeleton was set to 0.2 to include the WM tracts that were common to all subjects. Individual FA maps were then projected onto this mean FA skeleton. The transformation matrix of FA obtained in the above steps was applied to MD maps.

2.5. Statistical methods

2.5.1. Structural MRI

Correlations between CSF-biomarkers and cortical thickness measures were performed using vertex-based GLM (general linear model) in FreeSurfer correcting for the effect of gender. For group comparisons of low Aβ-status (CSF Aβ42 levels ≤530 pg/mL) versus high Aβ-status (CSF Aβ42 levels >530 pg/mL), group was entered as a factor and the analyses were also corrected for the effect of gender. As all participants were 70-year old, no correction for age was included in the analyses. Years of education were not associated with cortical thickness and we did thus not correct for years of education in the models. The Gaussian smoothing kernel was 15 mm. The level of statistical significance was evaluated using a cluster-wise P (CWP) value correction procedure for multiple comparisons based on a Monte Carlo z-field simulation with a cluster forming threshold of $p < 0.05$ (vertex-z-threshold = 1.3).

The association between Freesurfer segmented subcortical volumes and CSF-biomarkers was assessed using univariate general linear models in SPSS (Armonk, NY: IBM Corp) correcting for gender and intracranial volume. Effect size of biomarker was assessed using Eta-squared [η2] (Richardson, 2011). The left and right side of the following subcortical volumes segmented in FS were included in the analysis: the lateral ventricle, gray matter of the cerebellum, the thalamus, the caudate, the putamen, the pallidum, ventral diencephalon, the hippocampus, the amygdala and the choroid plexus and further, the total volume of the third ventricle, and the fourth ventricle. In total, 16 measures of gray matter volume and 6 measures of ventricular spaces were used in the analysis. Thus, 22 models were used. A p-value of $p < 0.0027$ (i.e., 0.05 divided by 22) was considered as significant.

2.5.2. Diffusion tensor imaging

To assess the relationship between Aβ biomarkers with FA and MD maps, voxel-wise regression analyses were carried out including the Aβ markers as dependent variables and sex as a confounder. Moreover, the analysis was repeated for the above described subgroups while adjusting the analysis for gender. All analyses were performed using the randomize tool of FSL with 5000 permutations. The results were corrected for multiple comparisons using threshold-free cluster enhancement corrections ($p < 0.05$).

2.6. The influence of the APOE ε4 allele and of Aβ pathology

The correlation analyses between CSF Aβ38 and Aβ40 and brain structure were carried out, dividing the sample into the above described subgroups (APOE−/Aβ−, APOE+/Aβ−, APOE−/Aβ+, APOE+/Aβ+). As levels of Aβ42 is a defining factor in these 4 subgroups we did not perform correlation analyses between Aβ42 and brain morphology in the subgroups.

3. Results

3.1. The demographic characteristics of the investigated population

One hundred and five men and 108 women with CDR = 0 were included in the study. There were no significant sex differences regarding years of education, levels of Aβ38, Aβ40, Aβ42, Aβ42/Aβ40 ratio, P-tau or total tau levels (Table 1). Levels of CSF biomarkers were not associated with performance assessed by neuropsychological tests (data not shown).

From the original CSF sample (n = 318), 105 were excluded due to cognitive status or technical problems during image analysis. These were however not significantly different compared with the included sample regarding any of the investigated CSF biomarkers (results not shown). *APOE* ε2/ε3/ε4 genotypes were available for 210 subjects, and 71 (33%) were *APOE* ε4 carriers. These participants did not display differences in brain gray matter volume or white matter changes compared to participants without the ε4 allele. However, the presence of the ε4 allele was associated with reduced levels of Aβ42.

Table 1
Characteristics of the sample

	All		Men		Women	
Number	213		105		108	
APOE ε4	71		39		32	
APOE ε44	6		5		1	
Low Aβ42	51		26		25	
	Mean	Std	Mean	Std	Mean	Std
Age	70.55	0.27	70.57	0.25	70.52	0.28
Education	13.3	4.20	13.69	4.63	12.92	3.72
Aβ38	2515*	699	2451	669	2579	725
Aβ40	6255*	1411	6158	1372	6348	1447
Aβ42	721	223	714	226	727	222
Aβ42/Aβ40	0.087	0.021	0.086	0.022	0.088	0.02
P-tau	49.5	17.63	49.69	17.44	49.36	17.27
Tau	330.50#	137.26	337.48	139.54	323.71	135.23
NFL	874.46	640.72	869.85	424.75	878.98	800.08

Number; number of subjects; *APOE* ε4, number of participants with one *APOE* allele ε4; *APOE* ε44, number of participants with 2 *APOE* allele ε4; Low Aβ42number of participants with low CSF $A\beta_{1\text{-}42}$; Age; age in years; Education, education in years; NFL, neurofilament light; *: significantly reduced in participants with low Aβ42 ($p < 0.05$); #: significantly increased in participants with low Aβ42 ($p < 0.05$); CSF biomarkers reported in pg/mL.

3.2. Demographic and biomarker characteristics in the APOE−/Aβ−, APOE−/Aβ+, APOE+/Aβ− and APOE+/Aβ+ groups

One hundred and sixteen participants were APOE−/Aβ−, 23 were APOE−/Aβ+, 44 were APOE+/Aβ−, and 27 were APOE+/Aβ+. The APOE−/Aβ+ group had lower levels of CSF Aβ38 than the APOE+/Aβ− group. The APOE+/Aβ− groups had higher Aβ38 levels compared to the APOE+/Aβ+. The same differences between subgroups were found for levels of Aβ40, with the exception that Aβ40 were not significantly different in the comparison between APOE−/Aβ− and APOE−/Aβ+. The APOE−/Aβ− group had higher levels of CSF Aβ42 than all other subgroups. Aβ42 was further higher in APOE+/Aβ− compared to the APOE−/Aβ+ group.

P-tau and total tau were lower in the APOE−/Aβ− group compared to the APOE+/Aβ− and APOE+/Aβ+ groups (Table 2). The 4 subgroups did not display significant difference on any neuropsychological test (results not shown).

3.3. Correlations between CSF Aβ38, Aβ40 and Aβ42 and brain structure and diffusion tensor data in the whole sample

Fifty-one of 213 (24%) participants had Aβ pathology in the brain (i.e., had CSF Aβ42 levels ≤530 pg/mL). Aβ pathology was associated with low levels of Aβ38 and Aβ40 and higher levels of total Tau. CSF Aβ42 levels or Aβ42/Aβ40-ratio analyzed as continuous variables were not associated with cortical or subcortical volumes. Participants with Aβ pathology did not display reduced cortical and subcortical volumes compared to participants without Aβ pathology.

Aβ38 was positively correlated with cortical thickness in a total area of 12,245 mm^2 of the cortical mantle. Significant correlations were found in clusters in the left superior frontal-, posterior cingulate-, precuneal-, lingual- and pericalcarine cortex and in the right hemisphere in the insular-, superior temporal-, supramarginal-, entorhinal-, lingual- and, pericalcarine cortex (Fig. 1A, supplementary, Table s.1). Further, Aβ38 was positively correlated with the volume of the left and right thalamus. CSF Aβ38 was also negatively correlated with the ventricular and the bilateral choroid plexus volumes (Table 3).

Aβ40 was positively correlated with cortical thickness in a total area of 11,067 mm^2 of the cortical mantle. Significant correlations were found in clusters in the left lingual-, pericalcarine-, posterior cingulate-, precuneal-, superior frontal cortex and in clusters in the right supramarginal-, insular-, superior temporal-, entorhinal-, pericalcarine- and, lingual cortex (Fig. 1B, Supplementary Table s. 2). Further, Aβ40 levels was positively correlated with the volume of the left and right thalamus. CSF Aβ40 was also negatively correlated with the ventricular and, choroid plexus volumes (Table 3).

The voxel-based analyses of white matter changes did not reveal any significant correlations with CSF Aβ42 levels or Aβ42/Aβ40-ratio analyzed as continuous variable or when participants with Aβ-pathology were compared with participants without Aβ-pathology.

FA was significantly positively correlated with CSF Aβ38 levels in areas of the inferior fronto-occipital fasciculus, the superior longitudinal fasciculus and the inferior longitudinal fasciculus. Negative correlation was also found in small areas of the corticospinal tract and, the superior longitudinal fasciculus. MD was negatively correlated with Aβ38 levels areas in clusters in the anterior thalamic radiation, the corticospinal tract, the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and, the superior longitudinal fasciculus (temporal part) (Fig. 2A, Supplementary Table s.3).

CSF Aβ40 levels was significantly positively correlated with FA in areas of the inferior fronto-occipital fasciculus, the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the anterior thalamic radiation and the cingulum. Aβ40 was further negatively correlated with FA in small areas in the corticospinal tract and the superior longitudinal fasciculus. Aβ40 was also negatively correlated with MD in areas in the forceps minor, the anterior thalamic

Table 2
Differences between amyloid and APOE subgroups

	APOE−/Aβ− (1)	*APOE*−/Aβ+ (2)	*APOE*+/Aβ− (3)	*APOE*+/Aβ+ (4)
n	116	23	44	27
Men/women	55/61	10/13	23/21	16/11
Age	69,71 (0,30)	70,59 (0,23)	70.59 (0,24)	70,54 (0,15)
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Education	13,73 (4,61)	13,09 (3,34)	12,16 (3,56)	13,54 (3.87)
Aβ38	2528,32 (652,50)	2249,61 (674,66) b**	2715,48 (711,84) c*	2376,63 (829,06)
Aβ40	6299 (1291,21)	5733,96 (1566,37) b*	6653,95 (1431,327) c*	5878,89 (1605,87)
Aβ42	844,25 (148,23) a**, d**, e**	441,52 (82,31) b**	748,07 (150,254) c**	388,70 (85,70)
p-tau	46,96 (14,29) d*. e*	47,61 (16,10)	53,39 (19,28) c**	56,44 (25,343)
tau	303,75 (96,13) d*. e*	331,61 (138,39)	364,44 (158,817)	391,56 (206,67)
nfl	969,57 (1171,68)	746,18 (332,16)	899,32 (820.78)	938,26 (481,66)
neurogranin	199,10 (63,80)	199,71 (65,56)	222,08 (79,07)	208,18 (80,36)

Key: Sd, standard deviation; a, significantly different between group 1 & 2; b, significantly different between group 2 & 3; c, significantly different between group 3 & 4; d, significantly different between group 1 & 3; e, significantly different between group 1 & 4; *, $p < 0.05$; **, $p < 0.01$; n, number; Age, age in years; education, education in years; CSF biomarkers reported in pg/mL.

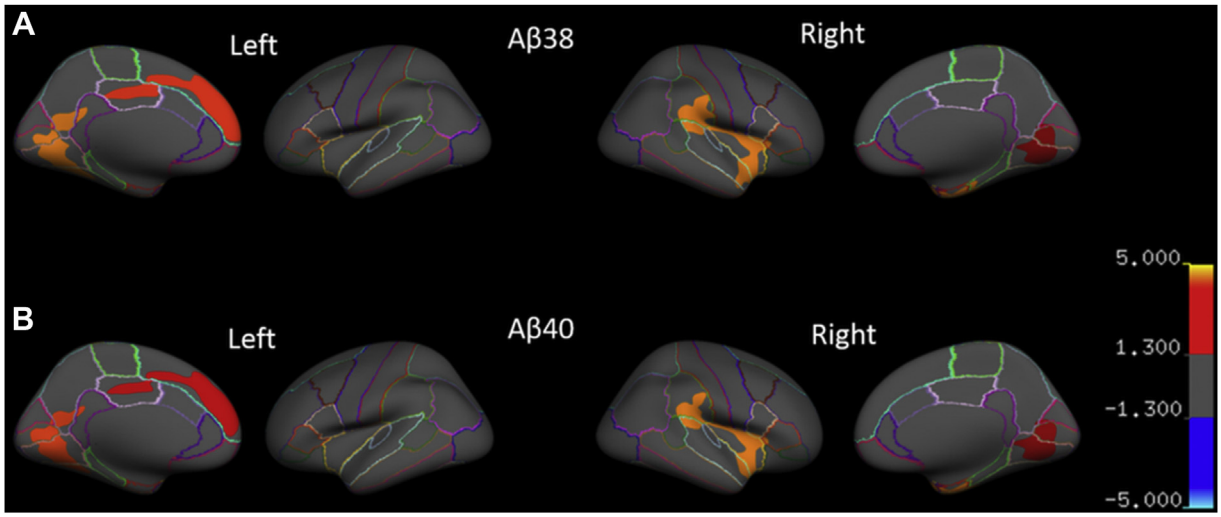

Fig. 1. The correlation between CSF Aβ38 (A) and Aβ40 (B) in the whole sample. Correlation displayed on the inflated cortical surface. Warmer colors indicate a positive correlation between the CSF biomarker and cortical thickness. To the left, left- and to the right, right-hemisphere, cluster-wise *p*-value <0.05 are displayed.

radiation, the uncinate fasciculus, the superior longitudinal fasciculus, the superior longitudinal fasciculus (temporal part), the cingulum, the forceps major, the inferior fronto-occipital fasciculus, the corticospinal tract and, the inferior longitudinal fasciculus (Fig. 2B, Supplementary Table s.3).

3.4. Correlations between CSF Aβ38 and Aβ40 and structural and diffusion tensor data in APOE−/Aβ− participants

Among individuals without Aβ pathology and without the *APOE ε4* allele, Aβ38 was positively correlated with cortical thickness in a total area of 7577.2 mm^2 in clusters in the left supramarginal gyrus, left anterior insula, left anterior temporal gyrus, the left temporal parietal junction, right anterior insula, anterior superior temporal gyrus, and a small part of right supramarginal gyrus (Fig. 3A, Supplementary Table s.4).

Subcortical associations with CSF Aβ38 included negative correlations with the bilateral volumes of the lateral ventricle, with the volume of fourth ventricle and with the bilateral volumes of choroid plexus. Positive association was observed for the volumes of bilateral thalamus, however the association was only borderline significant for the left thalamus ($p = 0.004$), the bilateral accumbens area, and the left hippocampus (Table 4).

Correlation between Aβ40 and subcortical volume and cortical thickness were essentially found in the same regions as for CSF Aβ38, except that we did not find positive correlation with thickness in the right supramarginal gyrus (Fig. 3B, Supplementary Table s.5), and further that we did not find significant association between Aβ40 and the volume of left hippocampus (Table 5). Aβ38 was also positively correlated with FA in areas of the forceps major, the forceps minor, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus, Superior longitudinal fasciculus (temporal part), the cingulum hippocampal part and the corticospinal tract. Further was Aβ38 negatively correlated with MD in the cingulum, the forceps minor, the anterior thalamic radiation, the inferior fronto-occipital fasciculus, the uncinate fasciculus, the forceps major (Fig. 4A, Supplementary Table s.6).

CSF Aβ40 were positively correlated with FA in areas of the anterior thalamic radiation, the cingulate gyrus, the forceps minor, the inferior fronto-occipital fasciculus, the uncinate fasciculus, the forceps major and the inferior longitudinal fasciculus. FA was also negatively correlated with Aβ40 in small areas of the corticospinal tract and the superior longitudinal fasciculus (Fig. 4B, Supplementary Table s.6).

Table 3
The variance of subcortical volumes explained by CSF biomarkers in the total sample

Aβ38	*p*	All η^2	B	Aβ40	*p*	All η^2	B
L LV	$p < 0.001$	0.127	−3.245	L_LV	$p < 0.001$	0.137	−1.668
L TH	$p = 0.001$	0.050	0.266	L_TH	$p = 0.002$	0.046	0.106
3V	$p < 0.001$	0.074	−0.203	3V	$p < 0.001$	0.075	−0.101
4V	$p < 0.001$	0.089	−0.254	4V	$p < 0.001$	0.094	−0.129
L CP	$p < 0.001$	0.170	−0.182	L_CP	$p < 0.001$	0.165	−0.089
R LV	$p < 0.001$	0.920	−2.905	R_LV	$p < 0.001$	0.093	−1.444
R TH	$p < 0.001$	0.061	0.183	R_TH	$p = 0.001$	0.054	0.085
R CP	$p < 0.001$	0.190	−0.261	R_CP	$p < 0.001$	0.188	−0.128

Key: L, left; R, right; inferior lateral ventricle; LV, lateral ventricle; TH, thalamus; 3V, third ventricle; 4V, fourth ventricle; AC, accumbens area; CP, choroid plexus; η^2, etasquared; B, parameter estimates; *p*, *p*-value.

3.5. Correlation between CSF Aβ38, Aβ40 and brain structure and diffusion tensor data in data in APOE−/Aβ+ participants

Among participants without the *APOE ε4* allele with Aβ pathology, levels of CSF Aβ38 was positively correlated with cortical thickness in a 2070 mm^2 area encompassing the left lingual and fusiform gyrus (Fig. 3A, Supplementary Table s.7). No significant correlation was found on the right side, or with Aβ40 bilaterally. Further were both levels of CSF Aβ38 and CSF Aβ40 negatively correlated with the volume of the lateral ventricle and with the right choroid plexus (Tables 4 and 5). No significant correlation with diffusion tensor imaging data was found.

3.6. Correlation between CSF Aβ38, Aβ40 and brain structure and diffusion tensor data in in APOE+/Aβ− participants

In APOE+/Aβ− participants CSF Aβ38 was positively correlated with cortical thickness in 13119,36 mm^2 of the cortical mantle, in posterior middle frontal gyrus and precentral gyrus and lingual bilaterally, in the medial surface of left superior frontal gyrus, posterior cingulate, precuneus, in the left inferior parietal cortex, and in the left supramarginal gyrus (Fig. 3A, Supplementary Table s.8).

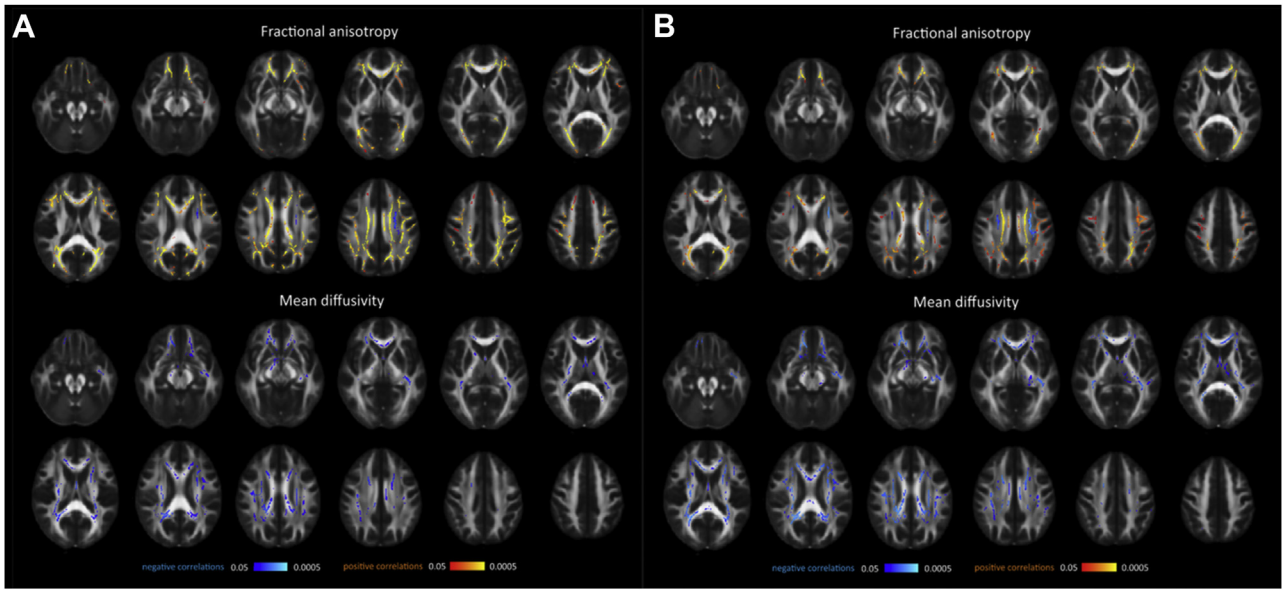

Fig. 2. The correlation with CSF Aβ38 (A) and CSF Aβ40 (B) and white matter tracts of the brain in the whole sample. Cold colors, areas of significant negative correlation, darkest blue = $p < 0.05$ brightest blue = $p < 0.005$. Warm colors, areas of significant positive correlation, darkest red = $p < 0.05$ brightest red = $p < 0.005$.

The correlation with CSF Aβ40 revealed very similar results but with additional areas in the left superior parietal cortex and in the supramarginal gyrus, all together encompassing an area of 15421,67 mm^2 of the cortical mantle (Fig. 3B, Supplementary Table s.9). Only the volume of left choroid plexus was negatively correlated with CSF Aβ38 and CSF Aβ40 (Tables 4 and 5). No significant correlation with diffusion tensor imaging data were found.

3.7. Correlation between CSF Aβ38, Aβ40 and brain structure and diffusion tensor data in APOE+/Aβ+ participants

In APOE+/Aβ+ participants CSF Aβ38 was negatively correlated with cortical thickness in 7955,36 mm^2 of the cortical mantle in areas that included the left superior and inferior parietal cortex as well as the right postcentral, inferior temporal gyrus and the right precuneus (Fig. 3A, Supplementary Table s.10). The correlation with CSF Aβ40 was essentially found in the same areas as for Aβ38 however encompassing a larger area 9019,33 mm^2 of the cortical mantle (Fig. 3B, Supplementary Table s.11). CSF Aβ38 and Aβ40 was negatively correlated with the volume of the right amygdala (Tables 4 and 5).

Further, CSF Aβ38 was positively correlated with FA in areas of the anterior thalamic radiation, the forceps major, the forceps minor, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus and the uncinate fasciculus, and negatively correlated with MD in the anterior thalamic radiation, the forceps minor, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the superior longitudinal fasciculus (Fig. 5A, Supplementary Table s.12).

CSF Aβ40 revealed significant positive correlation with FA in the same regions as found for Aβ38, except we did not find correlation with areas in the uncinate fasciculus. Further, CSF Aβ40 was negatively correlated with MD in the same tracts as found for Aβ38 (Fig. 5B, Supplementary Table s.12).

4. Discussion

We investigated CSF levels of Aβ38, Aβ40, Aβ42 and Aβ42/Aβ40 ratio in relation to MRI changes in cortical thickness, subcortical volumes and white matter changes, in a Swedish population of cognitively normal 70-year olds. Traditional measures of amyloid pathology, such as low Aβ42 or Aβ42/Aβ40 ratio, were not associated with changes in the grey- or white matter of the brain. However, low levels of Aβ38 and Aβ40 were associated with reduced cortical thickness, smaller subcortical volumes and decreased integrity in brain white matter tracts in the whole sample. These results suggest that Aβ38 and Aβ40 might be better markers of brain structural integrity than Aβ42 and Aβ42/Aβ40 in cogitively normal 70-year olds.

A positive association between Aβ38, Aβ40 and brain structure was also found in 3 of 4 of the analyzed subgroups (in Aβ−/APOE−, Aβ+/APOE−, Aβ−/APOE+). *APOE* ε4 allele carriers with Aβ-pathology did however display negative correlations with Aβ38 and Aβ40 regarding subcortical and cortical gray matter volumes, while the correlation was positive regarding FA and negative with MD. Thus, higher levels of Aβ38 and Aβ40 seem to be linked to better preserved white matter but smaller gray matter volume in the brains of these participants. As this group already has Aβ-dysregulation that are manifested by the presence of Aβ-plaque pathology in the brain, it seems conceivable these participants are vulnerable to high Aβ-production, reflected by high CSF Aβ38 and Aβ40 levels.

A possible interpretation of our results is that Aβ+/APOE+ group may have had Aβ-pathology longer than participants with Aβ+/APOE− and that structural brain changes have had time to develop in the former but not the latter group. If these results are related to different stages in a disease process, it might be that gray matter changes caused by Aβ-dysregulation may precede white matter changes. Our results support Kantarci et al. findings showing that white matter changes related to Aβ-pathology were only detectable in people with gray matter atrophy.

Associations between low levels of Aβ38 and Aβ40 and brain structural measures, in particular cortical thickness, have to the best of our knowledge not been previously reported in cognitively normal subjects. One possible explanation for the results is that participants in this cohort were relatively old. Several studies have shown that atrophy in gray and white matter increases with age (Christiansen et al., 1994; Raz et al., 2004). Thus, in this cohort of 70-year olds, there may be a sufficient number of people having

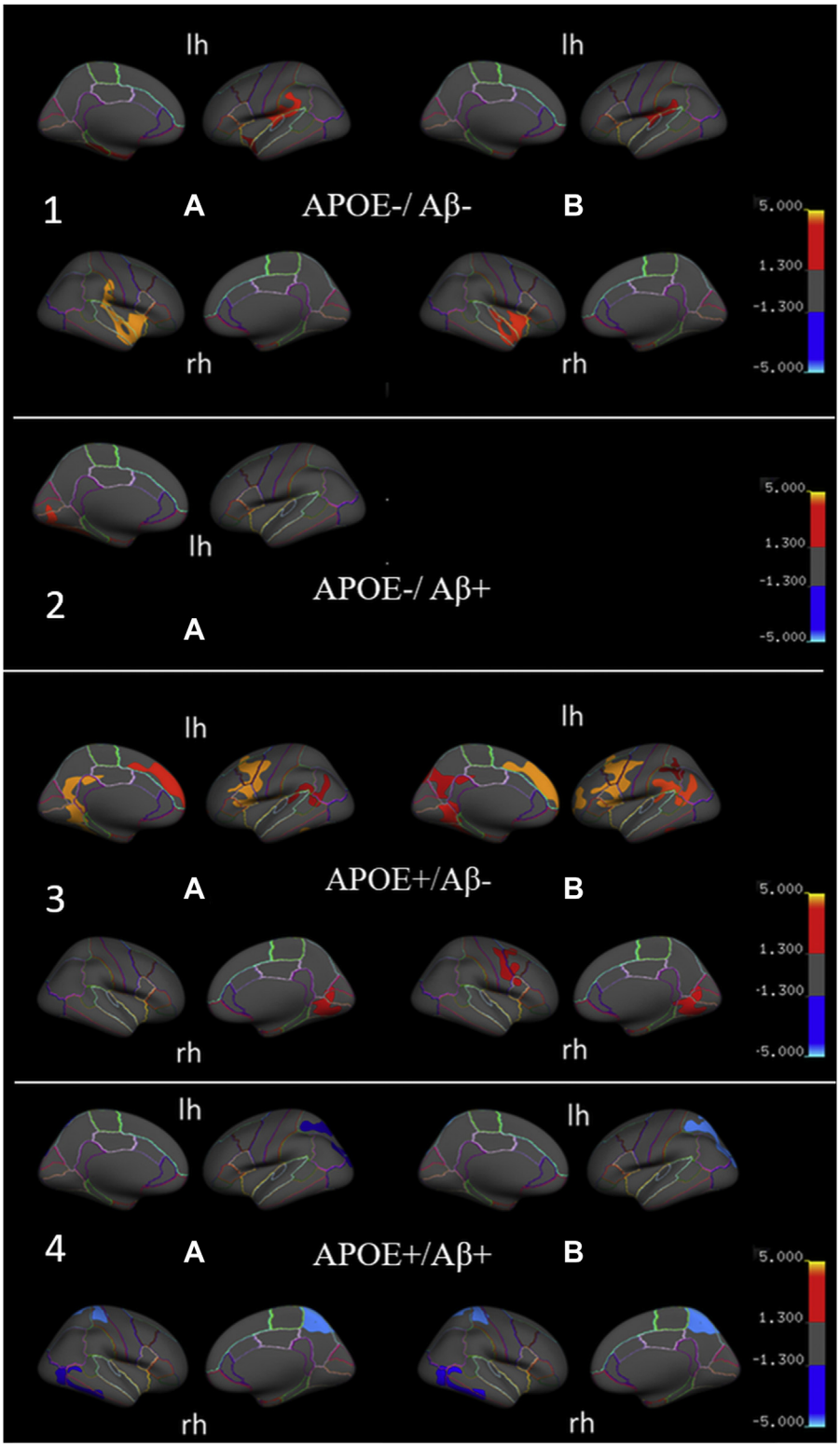

Fig. 3. The correlation between CSF Aβ38 (A) and Aβ40 (B) and cortical thickness in Aβ−/APOE−, Aβ+/APOE−, Aβ−/APOE+ and Aβ+/APOE+. Correlation displayed on the inflated cortical surface. Warmer colors indicate a positive correlation between the CSF biomarker and cortical thickness. Above-left below right hemisphere, cluster-wise *p*-value <0.05 are displayed.

enough brain atrophy to detect an association with CSF Aβ38 and Aβ40. There are several possible explanations for our findings. First, the associations may reflect non-AD processes. Low levels of CSF Aβ40 have been associated with the presence of other pathologies, such as cerebral amyloid angiopathy (CAA) (Chen et al., 2018), white matter lesions (Selnes et al., 2010) (Skoog et al., 2018) or subcortical injury (van Westen et al., 2016) (Janelidze et al., 2016). Moreover, low levels of CSF Aβ38 (Heywood et al., 2018) and low levels CSF of

Table 4
The variance of subcortical volumes explained by CSF Aβ38 in the subdivided sample

Aβ38	*p*	*APOE*−/Aβ−		*p*	*APOE*−/Aβ+		*p*	*APOE*+/Aβ−		*p*	*APOE*+/Aβ+	
		η^2	B		η^2	B		η^2	B		η^2	B
L LV	<0.001	0.105	−2.99	0.006*	0.355	−7.73	ns			ns		
L TH	<0.004*	0.070	0.303	ns			ns			ns		
4V	<0.001	0.136	−0.328	ns			ns			ns		
L HC	=0.002	0.079	0.172	ns			ns			ns		
L AC	=0.001	0.330	0.061	ns			ns			ns		
L CP	<0.001	0.124	−0.179	ns			=0.001	0.232	−0.204	ns		
R LV	=0.001	0.089	−2.853	=0.001	0.543	−10.581	ns			ns		
R TH	<0.001	0.106	0.280	ns			ns			ns		
R AM	ns			ns			ns			0.003*	0.338	−0.182
R AC	=0.003*	0.078	0.043	ns			ns			ns		
R CP	<0.001	0.183	−0.290	<0.001	0.541	−0.526	ns			ns		

Key: L, left; R, right; LV, lateral ventricle; TH, thalamus; 4V, fourth ventricle; HC, hippocampus; AM, amygdala; AC, accumbens area; CP, choroid plexus; η^2, etasquared; B, parameter estimates, *p*, *p*-value; ns, not significant; * not significant after correction for multiple comparisons.

Aβ38 and Aβ40 (Gabelle et al., 2011) have been found in patients with frontotemporal dementia. The low levels of Aβ38 and Aβ40 may thus be unspecific markers for neuronal dysfunction. In line with a previous study (Janelidze et al., 2016), we found that CSF Aβ38 and Aβ40 correlated with non-AD-specific subcortical changes, such as larger ventricles and white matter changes in the total sample. We additionally found significant correlations with the volume of the bilateral thalamus. Contrary to findings by Janelidze et al., CSF Aβ42/Aβ40-ratio or Aβ42 alone did not predict hippocampal volume in this cohort. It seems likely that the explanation for this difference is that mentioned study included patients with mild cognitive impairment and dementia while our sample consists only of cognitively normal subjects, thus a potential negative effect Aβ pathology may not have occurred yet in our sample.

Second, it might also be related to the AD process. Decreased CSF levels of all Aβ species have been linked to reduced neuronal activity (Cirrito et al., 2005; Kamenetz et al., 2003; Yamamoto et al., 2015), which may be caused by cortical and subcortical injury and loss of neurons (Janelidze et al., 2016). The low levels of Aβ38 and Aβ40 found in individuals without amyloid pathology in our study might then reflect neuronal dysfunction occurring at a pre-amyloid phase of AD. It is interesting to note that we found the strongest associations between cortical thickness and low levels of CSF Aβ38 and Aβ40 in some regions that previously have been shown to accumulate Aβ-pathology early in preclinical AD, such as the posterior cingulate, precuneus and the insula (Palmqvist et al., 2017). It might be that these regions have a general sensitivity to dysregulation of various Aβ species. If our findings are related to AD, we suggest that it reflects a pre-amyloid stage of the sporadic form of AD. At this very early stage, occurring before amyloid pathology, subtle brain changes are related to lower levels of Aβ38 and Aβ40, maybe due to decreased production due to neuronal dysfunction. At a later stage, an increased APP-processing and increased Aβ production occur, maybe as a response to the subtle pathology associated with lower levels of Aβ38 and Aβ40. At this stage, increasing levels of Aβ38 and Aβ40 may identify individuals with increased APP-processing (and increased Aβ production) that may be associated with increased risk of Aβ pathology. This may explain the findings that high levels of these Aβ species may be early biomarkers for total production of Aβ (Wiltfang et al., 2007), and that very high levels may be risk factors for future development of Aβ pathology (Mattsson et al., 2016). At an intermediate stage, patients may be positive for Aβ pathology but not cognitively impaired. At this preclinical stage of AD, Aβ42 or Aβ42/40 ratio are direct markers of Aβ pathology, in contrast to Aβ38 and Aβ40 (Janelidze et al., 2016). As discussed above, Aβ pathology is usually not associated with gray or white matter atrophy in cognitively normal subjects. At a fourth stage, individuals will have Aβ pathology, cognitive symptoms, and brain atrophy. At this stage, CSF Aβ38 and Aβ40 may be related to degree of atrophy.

Low levels of Aβ40 may also be associated with cerebral amyloid angiopathy (Chen et al., 2018), which is a common early finding in AD. The animal study by Chen et al. found that low Aβ40 was associated with cortical thinning in areas that are affected in patients with CAA (Chen et al., 2018). We also found some similarities between the thinning associated with low CSF Aβ38 and Aβ40 in our study, and the pattern of cortical thinning reported in the sporadic form of CAA. Thus, common areas of regional thinning were found in the left midline surface of superior frontal gyrus, left precuneus, left posterior cingulate and bilateral supramarginal

Table 5
The variance of subcortical volumes explained by CSF Aβ40 in the subdivided sample

Aβ40	*P*	*APOE*−, Aβ−		*p*	*APOE*−, Aβ+		*p*	*APOE*+, Aβ−		*p*	*APOE*+, Aβ+	
		η^2	B		η^2	B		η^2	B		η^2	B
L LV	<0.001	0.113	−1.550	ns			ns			ns		
L TH	=0.003	0.074	0.155	ns			ns			ns		
4V	<0.001	0.145	−0.170	ns			ns					
L AC	=0.002	0.083	0.027	ns			ns			ns		
L CP	<0.001	0.113	−0.085	ns			<0.001	0.283	−0.112	ns		
R LV	=0.001	0.089	−1.432	=0.002	0.427	−3.922	ns			ns		
R TH	=0.001	0.100	0.1355	ns			ns			ns		
R AM	ns			ns			ns			=0.002	0.371	−0.098
R AC	<0.01	0.065	0.02	ns			ns			ns		
R CP	<0.001	0.161	−0.135	=0.002	0.45	−0.203	ns			ns		

Key: L, left; R, right; LV, lateral ventricle; TH, thalamus; 4V, fourth ventricle; AM, amygdala; AC, accumbens area; CP, choroid plexus; η^2, etasquared; B, parameter estimates, *p*, *p*-value; ns, not significant.

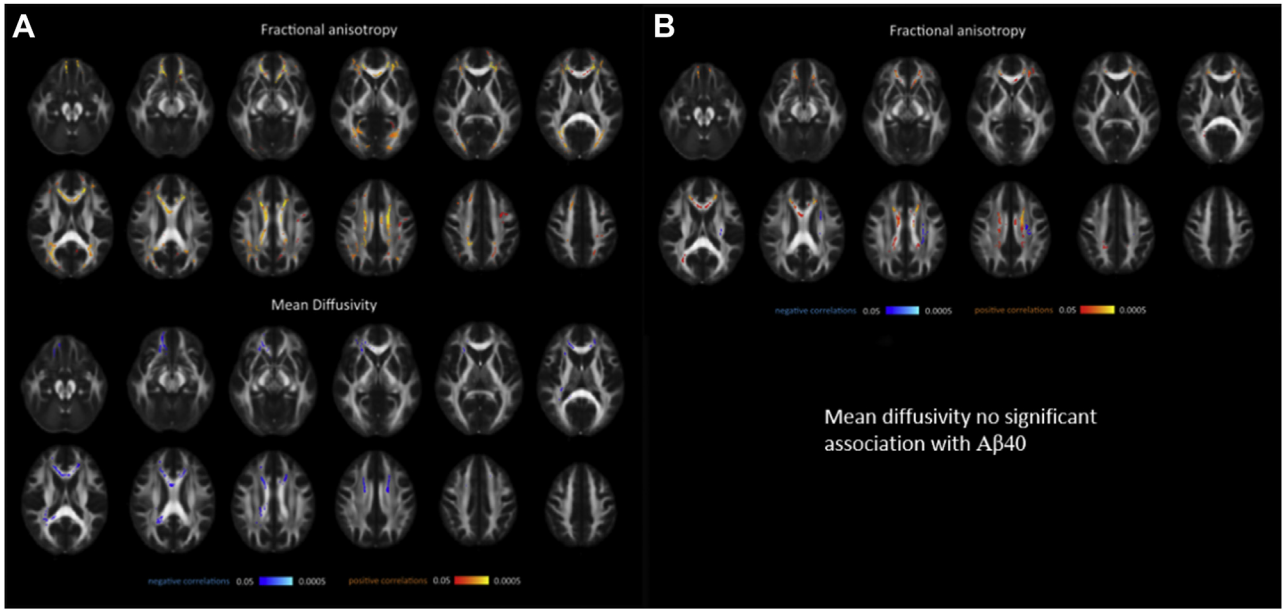

Fig. 4. The correlation with CSF Aβ38 (A) and CSF Aβ40 (B) and white matter tracts of the brain in Aβ−/APOE− Cold colors, areas of significant negative correlation, darkest blue = $p < 0.05$ brightest blue = $p < 0.005$. Warm colors, areas of significant positive correlation, darkest red = $p < 0.05$ brightest red = $p < 0.005$.

gyrus. However, contrary to our results, others report thinning bilaterally in all mentioned regions in sporadic CAA (Fotiadis et al., 2016). We also found that low levels of CSF Aβ38 and Aβ40, but not low Aβ42, were associated with increased MD and decreased FA in many white matter tracts in the brain. One previous study found that low CSF Aβ38 and Aβ40 were associated with white matter damage in various regions of the brain, while low CSF Aβ42 was associated with white matter damage in the temporal lobe (van Westen et al., 2016). Consistent with the findings by van Westen et al., our results suggest that low levels of CSF Aβ38 and Aβ40 may be predictors of general white matter integrity in large areas of the brain.

Among the strengths of our study are the comprehensive examinations and the homogeneous, and relatively large, sample of cognitively unimpaired individuals originating from a representative population-based study with CSF biomarkers and MRI. There are also some limitations. First, although the response rate was fairly high, only one fourth of the sample performed a lumbar puncture. Even though the CSF sample was similar to the total sample in terms of education and cognitive status, it differed on other factors. For example, more men than women performed a lumbar puncture (Rydberg Sterner et al., 2019). Second, even if the number of individuals with CSF and MRI data was relatively large, the overall number is low, which influences the statistical power.

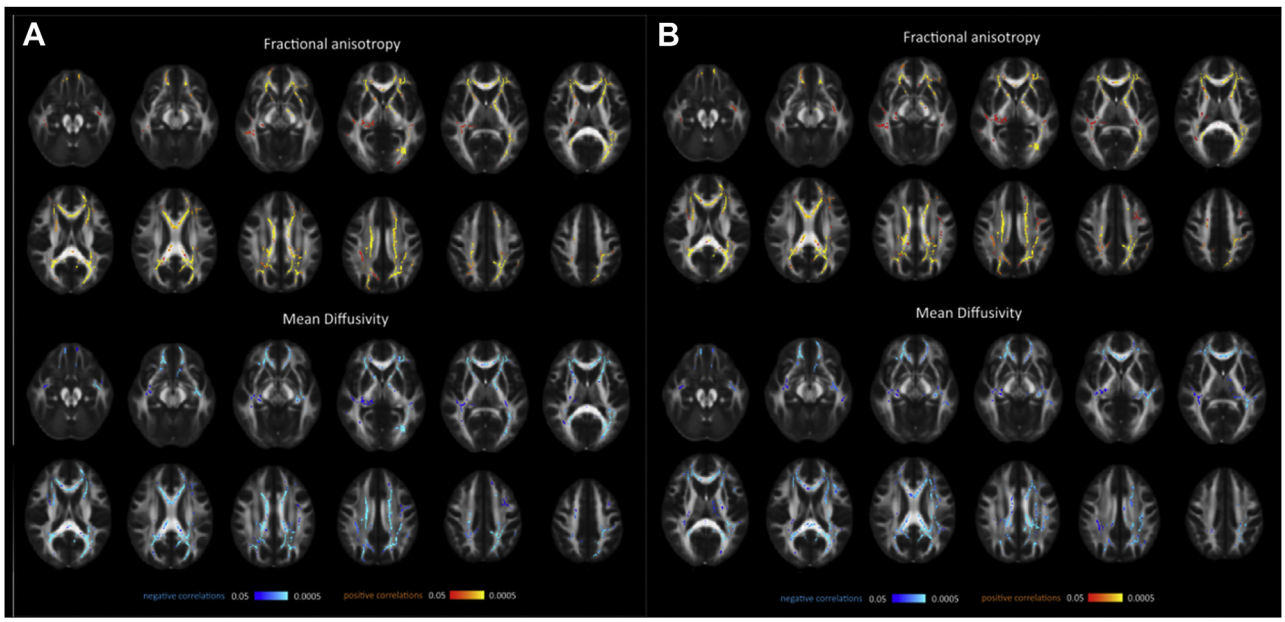

Fig. 5. The correlation with CSF Aβ38 (A) and CSF Aβ40 (B) and white matter tracts of the brain in Aβ+/APOE+. Cold colors, areas of significant negative correlation, darkest blue = $p < 0.05$ brightest blue = $p < 0.005$. Warm colors, areas of significant positive correlation, darkest red = $p < 0.05$ brightest red = $p < 0.005$.

Third, in the analysis of the DTI images, we used a traditional model that assumes a unique orientation of fibers in each voxel, which is represented by the tensor's main eigenvector (Mori and Tournier, 2014). However, using this technique, FA may also be reduced in areas with large orientation dispersion in white matter fibers (Szczepankiewicz et al., 2015). We found a negative correlation between Aβ38 and Aβ40 with FA in some small areas within a few large white matter tracts. We hypothesize that these findings in less than 10% of voxels significantly correlated with Aβ38 and Aβ40 may be a manifestation of the limitations in the technique used in this analysis. Our assumption is supported by findings for the other DTI parameter (MD) in which correlation with Aβ38 and Aβ40 was negative in 100% of significant voxels. A fourth limitation is that we do not have PET data available. In our hypothetical model, we assume that low levels of Aβ38 and Aβ40 is associated with ongoing neurodegeneration while high levels can be associated with the accumulation of Aβ fibrils in the brain. A potential positive association between Aβ38 and Aβ40 and Aβ fibrils can however not be studied in the present cohort. A fifth limitation is that we do not have longitudinal data. To be able to monitor changes in Aβ38 and Aβ40 over time and its relation to brain changes over time would provide better insights about how Aβ dysregulation may affect brain structure. Such longitudinal data may potentially also provide better understanding of the difference between high Aβ38 and Aβ40 associated with neuronal integrity in a healthy brain and high levels caused by Aβ over production. A final limitation is related to the fact that all participants are 70 years of age, and while our results are very robust in this cohort, further studies are needed to understand the generalizability of these results.

5. Conclusions

Our findings show that low CSF Aβ38 and Aβ40 are positively correlated with cortical thickness, subcortical brain volumes and white matter integrity in cognitively normal 70-year-olds. This positive correlation is also found in individuals with either Aβ pathology or APOE ε4 allele. For gray matter volume however, did individuals with both Aβ pathology and APOE ε4 allele display a negative correlation with CSF Aβ38 and Aβ40.

We hypothesize that low levels of CSF Aβ38 and Aβ40 are linked to a decrease of neuronal integrity, which may be associated with various underlying causes like aging, very early AD, vascular pathology or various forms of neurodegenerative diseases (e.g., frontotemporal dementia) or CAA.

We further hypothesize that individuals with both Aβ pathology and the APOE ε4 allele may have a general dysregulation of Aβ, which may explain the negative correlation between CSF Aβ38 and Aβ40 and cortical and subcortical brain volumes. Our results indicate that Aβ38 and Aβ40 levels could potentially be used to assess the degree of brain atrophy in cognitively normal individuals irrespective of its underlying cause. However, to confirm this hypothesis, more mechanistic studies, e.g., determining production and clearance rates of Aβ38 and Aβ40, need to be performed.

CRediT authorship contribution statement

Olof Lindberg: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Silke Kern:** Conceptualization, Writing - review & editing. **Johan Skoog:** Writing - review & editing. **Alejandra Machado:** Writing - review & editing. **Joana B. Pereira:** Formal analysis, Writing - review & editing. **Simona F. Sacuiu:** Writing - review & editing. **Lars-Olof Wahlund:** Conceptualization, Writing - review & editing. **Kaj Blennow:** Writing - review & editing. **Henrik Zetterberg:** Conceptualization, Writing - review & editing. **Anna Zettergren:** Writing - review & editing. **Eric Westman:** Conceptualization, Writing - review & editing. **Ingmar Skoog:** Conceptualization, Writing - review & editing.

Acknowledgements

Funding: 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), the Swedish Research Council (2012-5041, 2015-02,830, 2019-01,096, 2013-8717, 2017-00,639) Swedish Research Council for Health, Working Life and Wellfare (2013-1202, 2018-00,471, AGECAP, 2013-2300, 2013-2496), Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Hjärnfonden (FO2014-0207, FO2016-0214, FO2018-0214, FO2019-0163), Alzheimerfonden (AF-554461, AF-647651, AF-743701, AF-844671, AF-930868), Eivind och Elsa K:son Sylvans stiftelse. HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), and the UK Dementia Research Institute at UCL. KB is supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), Alzheimerfonden (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986), and European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236).

SK was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-81392, ALF GBG-771071). The Alzheimerfonden (AF-842471, AF-737641). The Swedish Research Council (2019-02,075), Stiftelsen Demensfonden, Stiftelsen Hjalmar Svenssons Forskningsfond, Stiftelsen Wilhelm och Martina Lundgrens vetenskapsfond, AZ was financed Alzheimerfonden (AF-930582), Demensförbundet, Magnus Bergvalls Stiftelse, Stiftelsen för Gamla tjänarinnor, Stiftelsen Hjalmar Svenssons Forskningsfond.

JBP is currently supported by grants from the Swedish Research Council (#2018-02201), Hjärnfonden (#FO2019-0289), Alzheimerfonden (#AF-930827) and the Strategic Research Program in Neuroscience at Karolinska Institutet (Stratneuro Startup Grant).

AM is supported by: Lindhès, Stohnes Stiftelsen och Stiftelsen for Gamla tjänarinnor. EW is supported by: FO2018-0222, AD fonden, AF-929650.

SFS was supported by the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG 637271) and Sahlgrenska Academy Homecoming Grant.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.10.033.

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