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Sluimer, J.D.

2011

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citation for published version (APA)

Sluimer, J. D. (2011). *Visualizing the Shrinking Brain: Longitudinal MR Studies in the Spectrum of Cognitive Decline*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Chapter 7

Whole-brain atrophy rate and CSF biomarker levels in MCI and AD: a longitudinal study

Neurobiology of Aging 2010

J.D. Sluimer
F.H. Bouwman
H. Vrenken
M.A. Blankenstein
F. Barkhof
W.M. van der Flier
Ph. Scheltens

Abstract

Objectives: To assess associations between cerebrospinal fluid (CSF) biomarker levels and MRI-based whole-brain atrophy rate in mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Methods: We included 99 patients (47 AD, 29 MCI, 23 controls) who underwent lumbar puncture at baseline and repeat MRI. A subgroup of 48 patients underwent a second lumbar puncture. CSF levels of beta-amyloid1-42 ($A\beta_{1-42}$), tau and tau phosphorylated at threonine-181 (P-tau₁₈₁), and whole-brain atrophy rate were measured.

Results: Across groups, baseline $A\beta_{1-42}$ and tau were modestly associated with whole-brain atrophy rate. Adjusted for age, sex and diagnosis, we found no association between $A\beta_{1-42}$ or tau, and whole-brain atrophy rate. By contrast, high CSF levels of P-tau₁₈₁ showed a mild association with a lower whole-brain atrophy rate in AD but not in controls or MCI patients. Finally, whole-brain atrophy rate was associated with change in MMSE, but change in CSF biomarker levels was not.

Conclusions: Whole-brain atrophy rate and CSF levels of $A\beta_{1-42}$, tau or P-tau₁₈₁ provide complementary information in patients with MCI and AD.

Introduction

Both cerebrospinal fluid biomarkers and magnetic resonance imaging are increasingly used to detect and characterise brain changes associated with Alzheimer's disease *in vivo*. In CSF, decreased A β_{1-42} levels and increased tau, and P-tau₁₈₁ levels are thought to reflect the presence of AD pathology.¹ These CSF biomarkers have been shown to differentiate patients with AD from control subjects with reasonable accuracy.³⁷ Moreover, these changes can be detected in patients with mild cognitive impairment (MCI) who will progress to AD.^{2;15} Brain tissue loss (atrophy) secondary to the neurodegenerative disease process can be visualized and measured using MRI. Whole-brain atrophy rate, measured from serial MRI, correlates well with disease and clinical progression in patients with MCI and AD.^{10;11;18}

Although both MRI and CSF biomarkers have been shown to be valuable markers of disease in MCI and AD^{36,37}, the relation between these markers has been less well studied. In cross-sectional studies, CSF biomarkers have been reported not to be related to MRI measures of atrophy, suggesting that these markers reflect different aspects of Alzheimer type neuropathology.^{25,26} However, longitudinal studies are needed, to clarify the relationship between these markers. The few studies that have reported CSF biomarkers and MRI measures in a longitudinal design, have used relatively small sample sizes, and have shown conflicting results in terms of whether or not these markers are associated.^{7,13,35}

The objective of the present investigation was to assess whether MRI measures and CSF biomarkers are related or provide independent information. We therefore assessed the relationship between baseline levels of CSF A β_{1-42} , tau, and P-tau₁₈₁ and whole-brain atrophy rate in patients with AD, MCI, and controls. In addition, we studied the association between longitudinal change of these CSF biomarker levels, whole-brain atrophy rates, and change in cognitive function.

Material and methods

Patients

We included 47 patients with AD, 29 patients with MCI and 23 controls with baseline CSF and repeat MRI scans from our memory clinic. All patients underwent lumbar puncture (LP) at baseline and MRI at baseline and follow up. At follow-up, 48 patients (20 AD, 17 MCI, 11 controls) agreed to undergo a second lumbar puncture. Follow-up time was defined as time between the two MRI scans (mean interval 1.7 years, standard deviation 0.7; range 11 m-4y). Patients underwent a standardized clinical assessment including medical history, physical and neurological examination, psychometric evaluation, and brain MRI. The Mini-Mental State Examination (MMSE) was used as a measure of general cognitive function.⁹ Diagnoses were established during a multidisciplinary consensus meeting according to the Petersen criteria for MCI²³ and the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable AD.¹⁹ The team involved in the diagnostic work-up was not aware of the results of the CSF analyses or the whole-brain atrophy rates. The control group consisted of 18 patients who presented to our memory clinic with subjective complaints, but who –after careful investigation- were considered to be cognitively normal. Additionally, we included 5 volunteers without cognitive complaints, who underwent the same diagnostic procedure as patients attending our memory clinic. The study was approved by the institutional ethical review board and all subjects gave written informed consent.

Clinical assessment at follow-up

Non-demented subjects (MCI and controls) visited the memory clinic annually (maximum: 4 visits). Diagnostic classification was re-evaluated at follow-up. The clinical diagnosis of dementia was determined according to published consensus criteria.^{19,21} Within the MCI group, 12 patients remained stable, and 17 progressed to AD¹⁹, one to fronto-temporal lobar degeneration (FTLD).²¹ Within the control group two patients with subjective complaints progressed to MCI, two to AD and one to FTLD, while 14 controls remained stable. Among the 48 patients with repeated LP, one control progressed to MCI (10 remained stable), and 11 patients with MCI progressed to AD, while 6 remained stable. The two patients converting to FTLD were excluded from analysis, leaving a sample size of 99 patients.

MRI

MR imaging was performed on a 1.0-T Siemens Magnetom Impact Expert scanner (Siemens AG, Erlangen, Germany) and included coronal T1-weighted 3D MPRAGE volumes (magnetization prepared rapid acquisition gradient echo; single slab 168 slices; matrix 256x256; FOV 250mm; voxel size 1x1x1.5 mm; repetition time=15ms; echo time=7ms; inversion time=300ms; flip angle 15°). All subjects included had two scans of adequate quality, performed on the same scanner using an identical imaging protocol. Scans were reviewed by a radiologist to exclude non-neurodegenerative pathology that could explain the cognitive impairment. Scans that fulfilled radiological criteria of the NINDS-AIREN for vascular dementia were excluded.³²

Whole-brain atrophy rates were measured with SIENA (Structural Image Evaluation, using Normalisation, of Atrophy), a fully automated technique part of FSL (for a detailed explanation see: www.fmrib.ox.ac.uk/analysis/research/siena).³¹ Briefly, the brain was extracted using the brain extraction tool.³⁰ Compared to standard SIENA, the procedure to remove non-brain tissue was slightly modified, because the brain extraction tool often leaves significant amounts of non-brain tissue (e.g. skull, meninges), while also removing cortex in some areas.¹⁶ To remove all non-brain tissue without losing cortex, we incorporated in the procedure the registration of a template mask to the individual scans. After this modified brain extraction procedure, the standard SIENA pipeline was continued. Using affine registration, the two scans were resampled in a common space to allow the change analysis. The skull was used as a scaling constraint in this step, in order to prevent the registration from introducing differences in head size between the two time points. The change analysis was then performed by applying automated tissue type segmentation, identifying edge points between brain tissue and other substances, and then estimating the perpendicular motion of the brain edge at these edge points. Finally, the average edge motion was converted to a percentage brain volume change (PBVC) between the two time points. For SIENA, an error of 0.15 to 0.20% on the PBVC scale has been reported.³¹ All individual scans, registration results, and SIENA output were reviewed by a rater who was blinded to the diagnosis.

CSF

CSF was obtained by LP between the L3/L4 or L4/L5 intervertebral space, using a 25-gauge needle, and collected in 12-mL polypropylene tubes. Within two hours, CSF samples were centrifuged at 2100g for 10 minutes at 4 °C. A small amount of CSF was used for routine analysis, including total cells (leucocytes and erythrocytes), total protein and glucose. CSF was aliquoted in polypropylene tubes of 0.5 or 1 ml, and stored at -80 °C until further analysis. CSF A β_{1-42} , tau and P-tau $_{181}$ were measured as described previously.³ The intra-assay coefficient of variation (CV) was 2.8% for A β_{1-42} , 3.7% for tau and 1.6% for P-tau $_{181}$. The inter-assay coefficient of variation (CV) was 13.5% for A β_{1-42} , 10.2% for tau and 12.8% for P-tau $_{181}$. To circumvent inter-assay variability, baseline and follow-up samples were run in the same assay at the time of the second spinal tap.⁴

Statistics

Statistical analysis was performed with SPSS 12.0 (2003, Chicago, IL). Whole-brain atrophy rate (PBVC), change in CSF biomarker levels, and change in MMSE over time were annualized by dividing by the time interval in years. A more negative whole-brain atrophy rate represents a larger relative brain volume loss per year. CSF biomarker levels were log-transformed. Frequency distributions for sex were compared with chi-squared tests. One way Analysis of Variance (ANOVA) adjusted for age and sex, with post hoc Bonferroni tests was used to compare continuous variables between the diagnostic groups. To assess associations between baseline CSF biomarker levels and whole-brain atrophy rate, we first calculated Pearson's correlations across the whole group. We then used linear regression analyses with baseline CSF biomarkers as independent variables, and whole-brain atrophy rate as dependent variable. We used three models, one for each CSF biomarker. Age, sex and diagnosis (using dummy variables) were entered as covariates. To check if associations with CSF biomarker levels differed according to diagnostic group, interaction terms (dummy-diagnosis * CSF biomarker) were included in the model. If there was a significant interaction between diagnosis and CSF biomarker ($p \leq 0.05$), β [SE] are displayed for each diagnostic group separately. When no significant interaction was found, the overall β is reported. Finally, associations between

annualized whole-brain atrophy rate, annualized change in CSF biomarker levels, and annualized change in MMSE score were assessed using bivariate correlations (available for 46 patients).

Results

Demographic and clinical data are presented by patient group in Table 1. MCI patients were older when compared to AD patients. We found no difference in sex or follow-up time. Annualized whole-brain atrophy rate differed between diagnostic groups ($p < 0.001$). We also found group differences for baseline $A\beta_{1-42}$ ($p < 0.001$), tau, and P-tau₁₈₁ (both $p < 0.01$). By contrast, annualized change in CSF c, tau, and P-tau₁₈₁ levels over time did not differ between patient groups (all $p > 0.49$).

To investigate associations between baseline CSF levels of $A\beta_{1-42}$, tau, and P-tau₁₈₁ and whole-brain atrophy rate, we first performed bivariate correlations across the whole sample, as shown in Figure 1. Lower baseline CSF levels of $A\beta_{1-42}$ ($r = 0.36$, $p < 0.001$) and higher tau levels ($r = -0.27$, $p < 0.01$) were associated with a higher whole-brain atrophy rate, while CSF P-tau₁₈₁ levels were not ($r = -0.16$, $p = 0.10$). After adjustment for age, sex, and diagnosis in linear regression analyses we found no association between $A\beta_{1-42}$ and whole-brain atrophy rate (β [SE] 0.34[0.26], $p = 0.19$). The interaction terms for CSF biomarker and diagnosis were significant for tau ($p = 0.02$) and P-tau₁₈₁ ($p = 0.02$), implying that associations of these CSF biomarkers and whole-brain atrophy rate were different for the diagnostic groups. In the control group there was a trend for increased tau to be associated with a higher whole-brain atrophy rate (β [SE] -0.62 [0.32], $p = 0.06$), however after exclusion of the two patients who progressed to AD the effect disappeared. Furthermore, this effect was not observed in MCI (β [SE] -0.39 [0.33], $p = 0.24$), or AD (β [SE] 0.43 [0.27], $p = 0.11$). By contrast, increased P-tau₁₈₁ levels were associated with a lower whole-brain atrophy rate (β [SE] 0.78 [0.35], $p = 0.03$) in the AD group. The effects in the control group (β [SE] -0.54[0.40], $p = 0.18$) and MCI group (β [SE] -0.52 [0.40], $p = 0.19$), though not significant, were in the opposite direction of that in the AD group.

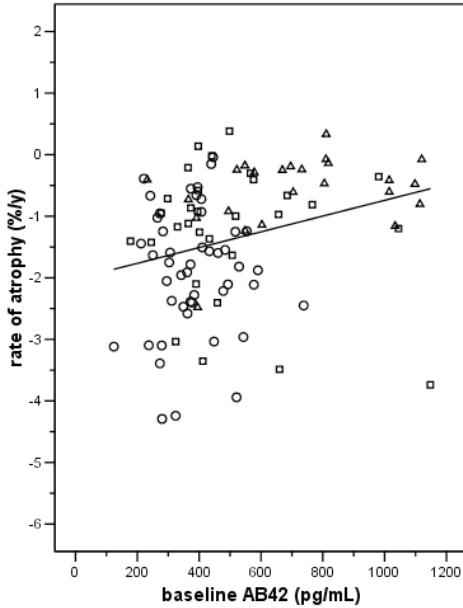
Finally, we studied associations between change in CSF biomarker levels over time, and whole-brain atrophy rate. Across groups, change in $A\beta_{1-42}$ ($r=0.02$, $p=0.90$), tau ($r=0.08$, $p=0.59$), and P-tau₁₈₁ ($r=0.06$, $p=0.68$) levels were not associated with whole-brain atrophy rate. In addition, we assessed longitudinal associations of change in CSF biomarker levels, whole-brain atrophy rate, and change in MMSE score over time. While whole-brain atrophy rate was associated with change in MMSE score ($r=0.43$, $p<0.01$), change in CSF levels of $A\beta_{1-42}$, ($r=0.18$, $p=0.23$), tau ($r=-0.03$, $p=0.83$), and P-tau₁₈₁ ($r=-0.07$, $p=0.96$) were not.

Table 1 Demographic and clinical variables by diagnostic group

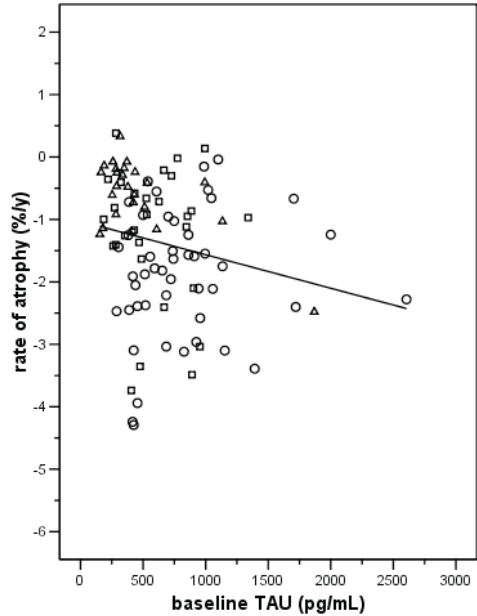
	Control	MCI	AD
N	23	29	47
Age-at-diagnosis (y)	66 (9)	71 (6)	65 (8) ^b
Sex (w/m)	11 / 12	15 / 14	25 / 22
Baseline MMSE score	29 (2)	26 (3) ^a	22 (5) ^{d,e}
Follow-up time (MRI) (y)	1.9 (1.0)	1.7 (0.6)	1.6 (0.5)
Time to last diagnosis (y)	2.2 (0.8)	1.8 (0.7)	-
Diagnosis at follow up	2 AD	17 AD	-
Baseline $A\beta_{1-42}$	696 (249)	481 (201) ^d	384 (119) ^d
Baseline tau	457 (390)	589 (286)	819 (463) ^c
Baseline P-tau₁₈₁	64 (34)	80 (33)	91 (34) ^c
Annualized change in CSF $A\beta_{1-42}$ level+	32 (68)	18 (35)	35 (32)
Annualized change in CSF tau level+	25 (43)	36 (52)	63 (129)
Annualized change in CSF P-tau₁₈₁ level +	1 (2)	2 (4)	0.0 (6)
Annualized whole-brain atrophy rate (%/y)	-0.6 (0.6)	-1.1 (1.0) ^a	-1.9 (1.0) ^{b,d}
Annualized change in MMSE score	-0.2 (1.1)	-1.5 (2.7) ^a	-2.2 (1.8) ^c

Data are presented as mean (sd), unless indicated otherwise. Differences between groups were assessed using ANOVA (age and sex as covariates where appropriate, post-hoc Bonferroni correction $p<0.05$). Please note that raw values are shown for CSF biomarkers (pg/mL), while log-transformed variables were used for statistical analysis. MCI=mild cognitive impairment; AD=Alzheimer's disease; FTLD=Frontotemporal Lobar Degeneration; MMSE=mini-mental state examination; CSF=Cerebrospinal fluid; $A\beta_{1-42}$ =beta-amyloid₁₋₄₂; P-tau₁₈₁=tau phosphorylated at threonine-181; MRI=Magnetic Resonance Imaging. ^a $p<0.05$ compared to controls; ^b $p<0.05$ compared to MCI; ^c $p<0.01$ compared to controls; ^d $p<0.001$ compared to controls; ^e $p<0.001$ compared to MCI + = longitudinal data available for 48 patients.

A



B



C

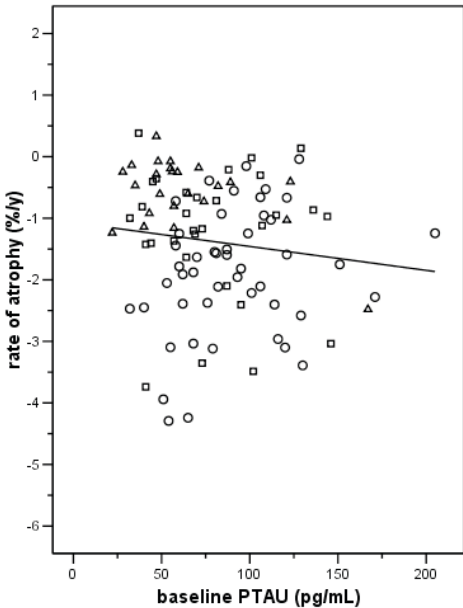


Figure 1. CSF biomarker levels and annualized whole-brain atrophy rates. Scatter plots of baseline CSF biomarker levels versus annualized whole-brain atrophy rate. (A.) Across diagnostic groups baseline $A\beta_{1-42}$ levels and whole-brain atrophy rate were associated ($r=0.36$, $p<0.001$). In diagnostic groups no association was found. (B.) Across diagnostic groups tau levels and whole-brain atrophy rate were associated ($r=-0.27$, $p=0.01$). In the control group there was a trend for increased tau to be associated with a higher whole-brain atrophy rate (β [SE] -0.62 [0.32], $p=0.06$). However, this effect disappeared when the three patients, who progressed to dementia were excluded. (C.) Across diagnostic groups P-tau₁₈₁ levels were not associated ($r=-0.16$, $p=0.10$). By contrast, there was a modest effect of an increased P-tau₁₈₁ level in the AD group (β [SE] 0.78 [0.35], $p=0.03$) being associated with a lower whole-brain atrophy rate.

_ = fit line across groups

Δ = controls; \square = MCI; \circ = AD

Discussion

The major finding of this study is that, notwithstanding modest correlations of baseline CSF biomarker levels and whole-brain atrophy rate across groups, hardly any association within diagnostic groups was found. Whole-brain atrophy rate was associated with clinical progression, measured by change in MMSE score, but longitudinal changes in the CSF biomarker levels were not. Thus, MRI and CSF biomarkers appear to reflect different aspects of AD: whole-brain atrophy rate appears to be linked to the clinical progression of the disease, whereas CSF biomarkers seem to reflect disease state rather than rate of progression.

Both CSF biomarker levels and atrophy on MRI are used in the diagnostic work-up of AD.^{10,36,37} Moreover, both marker types are predictive of dementia in patients with MCI.^{2,8,15,17} Previous studies typically report lowered CSF levels of $A\beta_{1-42}$, and elevated tau and P-tau, and higher rates of whole brain atrophy in MCI and AD.^{1,27} Our study confirms these results, which have been published previously in overlapping samples, derived from the same memory clinic population.^{3,29} Relatively few studies have combined CSF biomarker levels and atrophy measured from MRI, using a cross-sectional design^{2,25,26} or a longitudinal design.^{7,13,35} Of the longitudinal studies, one study described positive correlations between baseline CSF biomarkers and change in MRI measures in a group with a wide variation in cognitive impairment.³⁵ A second study described the relation between increase in tau phosphorylated at threonine-231 (P-tau₂₃₁) and $A\beta_{1-42}$ and decrease in hippocampal volume in seven patients with MCI.⁷ Finally, a study involving 22 AD patients found high baseline CSF levels of P-tau₂₃₁ to be associated with a higher rate of hippocampal atrophy.¹³ In the present study, however, we were not able to confirm these findings despite our larger patient sample.

For tau we found an association across groups with, as expected, higher levels of tau being related to a faster rate of atrophy; however we did not find this association within diagnostic groups. A trend towards higher tau being associated with higher whole-brain atrophy rates within the control group, could be ascribed to a few subjects showing clinical progression, since the effect disappeared after exclusion of three subjects who progressed to dementia. It might be argued that these subjects should not have been

included in the control group. However, because the risk of dementia increases with age, healthy elderly may progress to dementia.³³ Moreover, the cognitive continuum of dementia shows a gradual decline, and boundaries between AD and MCI are somewhat arbitrary.¹² We therefore think by including these progressing patients, we included the whole cognitive spectrum and studied a typical heterogeneous memory clinic population.

In contrast to $A\beta_{1-42}$ and tau, baseline P-tau₁₈₁ was weakly associated with whole-brain atrophy rate within the AD group, but not across groups. When we started this study, we hypothesised that patients with a larger load of senile plaques and neurofibrillary tangles (reflected by CSF biomarker levels), would have a higher rate of neuronal loss, consequently leading to a higher whole-brain atrophy rate. Our study did not confirm this. In fact, we found a modest effect in the opposite direction, with a higher (more abnormal) P-tau₁₈₁ being related to a lower (less abnormal) whole-brain atrophy rate. We are unsure how to interpret this finding. We cannot exclude the possibility that some of our AD patients were misdiagnosed, especially since no post mortem verification of diagnosis was available. However, all patients fulfilled NINDS-ADRDA clinical criteria for probable AD, which was confirmed both at baseline and at follow-up in multidisciplinary consensus meetings. Our findings might suggest the existence of subtypes of AD with differential combinations of levels of p-tau and atrophy rates. These results are comparable to our finding that, while for MCI patients the APOE ϵ 4 genotype is a predictor of faster subsequent progression, we observe the opposite in AD patients, as APOE ϵ 4 positive patients show a slower atrophy rate.²⁸ These results suggest that patients who – despite their favourable APOE ϵ 3 status – still develop AD, have a more aggressive form of the disease. Likewise, it seems that those who show clinical AD in spite of relatively low levels of p-tau, are likely to have slightly higher atrophy rates.

Post mortem studies have shown considerable overlap in the neuropathological features associated with AD, regardless of whether or not dementia was actually present during life.²⁰ This implies that other factors than senile plaques and neurofibrillary tangles must be involved in the development of the clinical syndrome of dementia. Indeed, it has been reported that brain volume

by itself is a good predictor of dementia, independent of senile plaque and neurofibrillary tangle load.²⁰ Our results are in line with these neuropathological findings, since we hardly found any association of whole-brain atrophy rates and CSF biomarker levels. This could imply that brain volume loss *in vivo*, measured with MRI, and CSF biomarker levels, which are thought to represent senile plaque and neurofibrillary tangle load, reflect different aspects of AD.

Among the strengths of this study is that we investigated the association of two widely used markers (CSF and MRI) in a large cohort of MCI, AD patients and controls derived from a memory clinic, in a prospective longitudinal fashion. For every patient, baseline CSF and longitudinal MRI were available. Follow up CSF data were available for a large subgroup. A limitation of this study may be that we used MRI scans that were obtained on a 1T scanner. We feel however that T1 scans have sufficient contrast of parenchyma-CSF, while the gain of scans obtained at a higher field strength largely lies in increased gray-white matter contrast. As we assessed the whole-brain, rather than gray and white matter separately, we feel that our scans had sufficient quality. In addition, it could be argued that hippocampal atrophy is a more specific marker for AD than whole-brain atrophy rate²⁴, which is increased in a number of different diseases that cause dementia.^{6,22} However, senile plaques and neurofibrillary tangles accumulate throughout the brain, and are not exclusively found in the medial temporal lobe.⁵ Our control group that included patients with subjective complaints may limit the generalisability of the results, since patients with subjective complaints are known to have an increased risk of progression to dementia.³⁴ However, the present study did not focus on differences between groups, but rather, on associations between two different types of biomarkers. We deliberately included the entire cognitive spectrum, and showed that – across the entire cognitive spectrum, MRI atrophy rate and CSF biomarkers were modestly correlated. Within diagnostic groups however, there was hardly any relationship. When healthy controls only would have been included, these results would be unaltered. Another possible limitation is our relatively high number of converters. All patients were assessed in a standardized way and diagnosed according to the criteria of Petersen.²³ Compared to the conversion rate of 12% per year reported by Petersen et al, the conversion rate of 59% over a period of almost two years in our group of MCI patients seems rather high.

However, our results are comparable to the conversion rate of other memory clinics¹⁴, while the conversion rate reported by Petersen et al was found in a general community setting.

In contrast to whole-brain atrophy rates which were associated with change in MMSE score over time, longitudinal changes in CSF biomarker levels were not. These results suggest that for tracking the rate of progression of AD, whole-brain atrophy rates are more useful than CSF levels of $A\beta_{1-42}$, tau, and P-tau₁₈₁; by contrast these CSF markers can be considered to be disease state markers, which may be more sensitive as diagnostic tools, possibly in earlier stages of AD.

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