**Visual evaluation of medial temporal lobe atrophy as a clinical marker of conversion from MCI to dementia and for predicting progression in patients with MCI and mild AD**

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**Short title:** Medial temporal lobe atrophy in predicting MCI and AD progression

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Background/Aims: To evaluate whether visual assessment of medial temporal lobe atrophy (vaMTA) can predict two-year conversion from MCI to dementia and progression of MCI and AD measured by the Clinical Dementia Rating Scale Sum of Boxes score (CDR-SB).

Methods: VaMTA was performed in 94 patients with MCI according to the Winblad criteria and 124 patients with AD according to ICD-10 and NINCDS-ADRDA criteria. Demographic data, the Consortium to Establish a Registry for Alzheimer’s Disease 10-word delayed recall, APOE-ɛ4 status, Cornell Scale for Depression in Dementia, and comorbid hypertension were used as covariates.

Results: VaMTA was associated with MCI conversion in unadjusted model but not in adjusted model (p=0.075), where delayed recall and APOE-ɛ4 status were significant predictors. With CDR-SB change as the outcome, an interaction between vaMTA and diagnosis (MCI/AD) was found, but in the adjusted model only delayed recall and age were significant predictors. For vaMTA below 2, the association between vaMTA and CDR-SB change differed between diagnostic groups. Similar results were found based on a trajectory analysis.

Conclusion: In adjusted models, memory function, APOE-4 status and age were significant predictors of disease progression, not vaMTA. The association between vaMTA and CDR-SB change was different in patients with MCI and AD.

**Keywords:** Mild Cognitive Impairment, dementia, Alzheimer disease, Clinical dementia rating scale, MRI, Medial temporal lobe atrophy, progression, conversion, visual assessment

**Introduction**

Alzheimer dementia (AD) is a serious condition affecting an increasing number of people worldwide [1]. The underlying neurodegenerative disease is characterized by three phases: a preclinical phase, a prodromal phase called mild cognitive impairment (MCI), and finally the dementia phase [2, 3]. The continuum of the disease has been in focus because therapeutic treatment trials should target patients early in the disease process, further highlighting the need for early diagnostic markers. To provide individualized information, treatment, and care for patients and caregivers, knowledge regarding the prognosis of MCI and AD is crucial.

Studies have found that 5–15% of patients with MCI will convert to dementia annually, but some patients never convert, and some revert to normal [4]. Several risk factors—both modifiable and non-modifiable—including comorbid diabetes mellitus, metabolic syndrome, low folate level, depression and neuropsychiatric symptoms, and increasing age have been found to predict MCI conversion [5, 6]. Hypertension has been found to be a risk factor for the development of dementia but not specifically as a marker of MCI conversion [5, 7]. Similarly, findings have been inconsistent concerning depression as a risk factor for MCI conversion, while it has been regarded as one of the most important modifiable risk factors for dementia development [5, 7].   
In addition, the degree of episodic memory impairment and biomarkers reflecting regional reduced glucose metabolism, altered levels of beta-amyloid and tau proteins in the CSF, APOE-ɛ4 genotype and atrophy detected on structural MRI have been found to predict conversion from MCI to AD [5, 8-10].   
While knowledge about predictors of MCI conversion is quite extensive, less is known about these markers’ ability to predict progression of AD [11]. The progression speed of AD differs among patients [12] and mean life expectancy varies from three to twelve years from diagnosis [13, 14]. Cognitive reserve, APOE-4 status, and biologically different AD subtypes have been suggested as possible explanations for the heterogeneity of the disease course [10, 11, 15].

The estimation of medial temporal lobe atrophy (MTA) on MRI scans, either visually assessed or evaluated through manual or automatic volumetry, has been found to be a valid marker for the conversion from MCI to dementia [16-18]. However, both manual and automatic volumetry methods lack clinical feasibility. In 1992, Scheltens et al. developed a visual assessment method for the clinical evaluation of MTA, which later demonstrated results comparable in accuracy to volumetric methods in separating AD patients from controls [19, 20]. If such clinically available MTA measurements could be used as both a marker of MCI conversion to dementia and a predictor of progression rate in MCI and mild AD, it would be clinically useful.

Thus, the aim of this longitudinal 24-month follow-up study was to explore: (1) if visually assessed MTA (vaMTA) could predict conversion from MCI to dementia in a heterogeneous geriatric and memory-clinic outpatient population, and (2) if vaMTA could predict global cognitive and functional decline as defined by an increase in the Clinical Dementia Rating Scale Sum of Boxes score (CDR-SB) in patients with MCI and mild AD.

**Materials and Methods**

***Participants***

A total of 555 patients from two memory clinics (n=352) and one geriatric outpatient clinic (n=203) were eligible for inclusion to a longitudinal multicenter study (main study not published yet). Criteria for inclusion included the following: patients diagnosed with cognitive impairment who spoke Norwegian, did not have serious comorbid diseases, had an informant, lived close enough to the centers to be reassessed, and who had the capacity to consent to the study. Of the included patients, 357 patients were followed up on average 24 months (16–37 months) after baseline, see flow chart (figure 1) for details.   
Analyses comparing followed-up and not-followed-up patients did not reveal any differences concerning cognitive or demographic measures, except that the followed-up patients had almost one more year of formal education.

[Fig. 1 near here]

In the present sub-study, we included patients with a baseline diagnosis of MCI or AD with mild degree of dementia according to the CDR (a score of 0.5 or 1.0) that had been assessed with a coronal section MRI of the brain within six months prior to or after the clinical examination at baseline (on average 2.0 months (SD 1.6) from baseline and in 85% of the patients less than 4 months between clinical examination and MRI), see flow chart.

***Baseline assessment***

At baseline, patients were assessed with a standardized examination protocol [21]. For the present MRI sub-study, we used the results from the Mini-Mental State Examination–Norwegian Revised Version (MMSE-NR), which measures global cognitive functioning on a scale from zero to 30, with a higher score denoting better cognitive functioning [22, 23]; and the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) 10-word delayed recall test (from here on, referred to as CERAD delayed recall) with scores between zero and 10, with a higher score denoting better delayed recall [24]. The Clinical Dementia Rating scale (CDR) was used as a global measure of cognitive and functional impairment. This instrument consists of six items (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) that can be scored 0, 0.5, 1, 2, or 3—the higher the score, the more severe the impairment—yielding a sum score between zero and 18 points called the CDR Sum of Boxes (CDR-SB) [25]. The six items were scored by one of the CDR certified co-authors (KP, MLB, or RSE) based on all available information from the patient and caregiver assessments [21]. In addition to the sum score, CDR yields a score reflecting the stage of dementia: 0 (no dementia), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), or 3 (severe dementia), based on an algorithm that gives priority to the memory item.   
To assess depressive symptoms during the previous week, the Cornell Scale of Depression in Dementia (CSDD) consisting of 19 items with possible scores zero to 2 was applied. The maximum sum score is 38 points; the higher the score, the more depressive symptoms are present [26]. Neuropsychiatric symptoms were registered with the Neuropsychiatric Inventory Questionnaire (NPI-Q), a 12-item informant scale rating the severity of neuropsychiatric symptoms on a scale from zero to 3, for a total score of zero to 36; the higher score, the more severe the neuropsychiatric symptoms are [27].   
APOE genotyping was conducted using the Illumina Infinium OmniExpress v1.1 chip at deCODE Genetics, Reykjavik, Iceland, and the result was dichotomized based on APOE-ɛ4 status (0 for no APOE-ɛ4 allele, and 1 if at least one allele was the APOE-ɛ4).

***Magnetic resonance assessments***

A skilled neuroradiologist (LC) with extensive experience in rating cerebral atrophy using the Scheltens MTA scale [28, 29] examined the MRI scans blinded to any clinical data. MTA assessment includes evaluation of the choroid fissure, the temporal horn of the lateral ventricle, and the height of the hippocampus, yielding a score of zero to 4, the higher the score the more atrophy [19]. MTA was assessed on both the left and the right side and a mean of the two sides was calculated. The MRI examinations had been conducted at several different MRI centers using different MRI protocols, all with coronal imaging of T1 (n=122) or T2 (n=98, of which 18 were T2/flair) for visual assessment of MTA. Of the 98 T2 images, 35 were patients with MCI, and 24 of these converted to dementia.

***Outcome at follow-up***

At follow-up, patients were assessed similarly as at baseline. The CDR-SB, which was the primary outcome, was rated by the same CDR-certified doctor as at baseline, blinded to the baseline CDR and baseline vaMTA scores.

***Diagnoses***

Patients were diagnosed at baseline and follow-up using all available information from the clinical assessments, blinded to the vaMTA ratings. The Winblad criteria were used for MCI [30], and the ICD-10 and NINCDS-ADRDA criteria were used for AD [31, 32]. Patients with mixed AD/vascular disease (n=5) were regarded as having AD.  
An interrater reliability analysis between two of the raters (MLB and KP) including 51 patients with eight different diagnoses from one of the memory clinics had been performed. It showed substantial to very good interrater agreement for MCI and early- and late-onset AD diagnoses (kappa=0.66, 0.73 and 0.85) [33]. Therefore, patients with MCI or AD from this memory clinic were diagnosed by one doctor alone (MLB or KP), and in cases of uncertainty, the diagnosis was discussed with a skilled professor of medicine (KE). Patients from the other two clinics were diagnosed by two doctors in consensus (MLB/KP + RSE/IS, or RSE + IS). At follow-up, all patients were diagnosed by two doctors in consensus (KP+KE, MLB+KE or RSE+IS).

***Statistical analysis***

The data were analyzed using IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA, and SAS v 9.4, Cary, NY, USA. Demographic and clinical characteristics between patient groups were compared using Student’s t-test for continuous data and χ2-test for categorical data. In the first part of the study, logistic and linear regression analyses were performed to explore which variables were able to predict conversion in patients with MCI and degree of progression in MCI and mild AD, respectively. Bivariate and multiple regression models were estimated. The dataset included patients from three different centers. To correctly adjust for possible cluster effect within the center, a logistic regression model for hierarchical data and a linear mixed model were estimated. The cluster effect appeared to be negligible in the adjusted models.   
In the second part of the study, a growth mixture model was estimated on CDR-SB measured at baseline and follow-up, with the aim of identifying unknown groups of patients following distinct trajectories, which could later be compared with regard to vaMTA. The groups were defined as distinct if the average group-belonging probability was above 0.7 and the 95% confidence intervals for trajectories were non-overlapping. The identified groups were compared with ANOVA and χ2-test. To assess the predictors of group belonging, nominal logistic regression analysis was conducted.  
All multiple regression models were reduced by Akaike’s Information Criteria (AIC) where the smaller value means a better model, and were adjusted for age and gender.

***Ethics***

The Regional Committees for Ethics in Medical Research in South-Eastern and Mid Norway approved the study (REK 2011/531). The patients and caregivers received oral and written information and gave written consent to participate. Only patients with the capacity to consent were recruited at baseline. For patients who lacked the capacity to consent at follow-up, their caregivers gave written consent.

**Results**

Table 1 shows the patient characteristics by diagnostic groups and by MCI sub-groups (converters and non-converters). The annual CDR-SB change was 0.91 (SD=1.55) in MCI patients and 2.14 (SD=2.01) in AD, while the MCI-to-dementia annual conversion rate (ACR) was 27%.

[Table 1 near here]

Comparing the 218 patients with MRI scans with the 77 patients without a valid MRI showed that patients with MRI had significantly lower MMSE scores and higher CDR-SB scores at baseline. Further, in the group that had MRI, fewer patients had hypertension (40% vs 53%, p=0.05), and a larger number had AD (57% vs 40%, p=0.012). None of the other variables listed in Table 1 differed significantly between patients with and without MRI scans. The proportion of patients with MCI converting to dementia did not differ significantly between those with and without MRI (56% vs 43%, p=0.151).

A logistic regression analysis showed a significant association between vaMTA and MCI conversion in the unadjusted model (OR=6.41, p=0.001), which disappeared after adjusting for other predictors (OR=3.58, p=0.075). CERAD delayed recall (OR=0.39, p<0.001) and positive APOE-ɛ4 status (OR=6.25, p=0.043) were predictors of conversion in the adjusted analysis (Table 2).

[Table 2 near here]

In exploring the value of vaMTA as a predictor of degree of progression in MCI and mild AD as measured by the annual CDR-SB change, a multiple linear regression analysis revealed a significant interaction between vaMTA and diagnosis (MCI/AD) in the unadjusted model (Table 3 and Fig. 2). Although the interaction term became non-significant in the adjusted model, the same tendency was observed. In addition, for values of vaMTA below 2.5 (below 2.0 in adjusted analysis) the annual CDR-SB change was higher in patients with AD than in patients with MCI.   
An interaction between CERAD delayed recall and diagnosis was assessed as well but was not significant in either unadjusted or adjusted analyses.  
Age and CERAD delayed recall were found to be significant predictors of degree of progression in the participants with MCI and mild AD in the adjusted model.

Some predictors were not included in the regression analyses; homocysteine and eGFR were available in only 164 of 218 patients (76 of the patients with MCI); the number of patients with delusions and hallucinations as measured by the NPI was small (n=39), as was the number of patients with diabetes (n=16).

[Table 3 and fig. 2 near here]

To explore the progression further, a trajectory analysis was carried out that resulted in four distinct progression groups (Fig. 3). The average probability of belonging to one of the groups was above 0.80 (0.87–0.93), and confidence intervals were non-overlapping, indicating well-defined groups. Significant differences in age, education, MMSE scores, CERAD delayed recall scores, vaMTA scores, and proportion of patients with MCI versus AD were found among the four groups (suppl. Table 1). Finally, a nominal regression model with group 1 (little progression) as the reference group was estimated (Table 4). In the adjusted model, having an AD diagnosis was a significant predictor of belonging to groups experiencing more progression, as were a lower CERAD delayed recall score and increasing age. The Cornell score was a predictor of belonging to a group with a quite stable CDR-SB (group 2) including more patients with AD and with higher baseline CDR-SB. VaMTA score was not a relevant predictor of group belonging in the adjusted model.

[Table 4 and fig 3 near here]

**Discussion**

We found an association between vaMTA and conversion from MCI to dementia that was no longer of significance (p=0.075) after controlling for other well-known predictive factors. Degree of memory impairment and APOE-ɛ4 status (carrier of ɛ4 allele) were predictors of conversion in the adjusted model. In the total cohort of patients with MCI and mild AD, memory impairment and increasing age were found to be predictors of greater progression as measured by the annual CDR-SB change, after adjusting for relevant covariates. An interaction between vaMTA and diagnosis (MCI/AD) was found in the unadjusted model that was no longer of significance in the adjusted model.

During follow-up, 59% of the patients with MCI converted to dementia, 27% annually, which is a high proportion compared to the generally reported 5–15% [4, 34, 35]. However, the diversity in reported ACRs is substantial, ranging between 2–31% in one review, with higher ACRs generally being found in memory-clinic cohorts as compared to community-dwelling volunteers [35].   
Several studies have found associations between vaMTA and MCI conversion [36-43]. The importance of vaMTA as a predictor alone, in addition to, or as compared to memory function has been debated. Some studies have concluded in favor of vaMTA [38, 41], and other studies favor memory impairment as the stronger predictor [40, 43]. Conflicting results might be due to the use of different statistical approaches or models not containing the same variables, making studies difficult to compare [38]. Furthermore, several studies have not included memory function as a covariate at all [36, 37, 39, 42]. Geroldi et al. showed that vaMTA was the only predictor of conversion after adjusting for other possible predictors but used MMSE and CDR-SB as covariates and no specific memory tests [42]. Korf et al. concluded that vaMTA was the only predictor of conversion after adjusting for memory impairment but did not include all the other analyzed predictors in the same model [38].  
It should be mentioned that, in the present study, after adjustment, vaMTA came close to being a predictor of conversion (p=0.075), and therefore, we suggest that the question as to whether or not vaMTA is a unique predictor of conversion from MCI to AD is still open.

The CDR-SB increased in both patients with MCI and AD, with a greater increase found in those with AD than those with MCI, a result in line with another study using CDR-SB as the primary outcome measure [44].   
We have found only one study using vaMTA as a predictor and a continuous measure of cognitive decline as an outcome measure [41]. No study assessed such an association in AD patients. In the study by Visser et al. (2002), vaMTA had an additive effect on the prediction accuracy of age and delayed recall [41].   
In the present study, exploration of the interaction between vaMTA and diagnosis (MCI/AD) suggests that in patients with MCI, a higher vaMTA score (more atrophy) is associated with a greater two-year increase in CDR-SB, while in AD, a higher vaMTA is associated with a smaller two-year increase in CDR-SB. One straightforward explanation could be that in a sub-group of patients with MCI, the vaMTA is a true predictor of degree of disease progression as measured with the CDR-SB. We hypothesize that the negative, or almost lacking, association between vaMTA and annual CDR-SB change found in AD could represent a ceiling effect of CDR-SB since in AD patients with a high vaMTA and a presumably high baseline CDR-SB, a further increase in the CDR-SB would be more difficult to achieve than an increase from a lower baseline score.   
The interaction analysis further showed that, for vaMTA below 2.0, patients with AD had a greater progression than patients with MCI for the same vaMTA values. A possible explanation could be that patients with AD with relatively little atrophy of the medial temporal lobe but possibly with atrophy in other brain regions, there is a more rapid cognitive and functional decline.

The trajectory analysis visualizes the progression diversity in this cohort. Memory, age, and AD diagnosis, but not vaMTA, were predictors of belonging to groups experiencing more progression than a group with a more stable course in adjusted analysis. In a study by Wilkosz et al. (2010) including only AD patients (mean MMSE of 21), six different progression groups were found, and cognitive impairment at baseline (MMSE), younger age, and psychotic symptoms were associated with a more rapid decline [45]. Our results are *partly* in line with this, memory impairment being an important predictor. However, we found that *increasing* rather than decreasing age was associated with belonging to a group experiencing more progression. A possible explanation for these contradictory findings is that the progression slope is not necessarily linear, and the disease stage might affect the results [11]. Surprisingly, the Cornell score was found to be a relevant predictor of belonging to a group with a higher proportion of patients with AD and higher baseline CDR-SB but who experienced relatively little progression (group 2) instead of group 1. One explanation for this finding could be that group 2 consisted of patients with early-phase, stable AD with well-preserved insight, experiencing reactive depressive symptoms [46].

The study has limitations. First, 77 (26%) of the patients enrolled in the study lacked a valid MRI from the baseline assessment. Exploratory analyses showed that patients with more severe cognitive impairment and patients with AD more frequently had a valid MRI examination, which is clinically understandable but might result in selection bias, as these patients also turned out to have a higher annual CDR-SB change than patients without MRI. Despite this obvious drawback, we think the results from this study are relevant to the daily clinical situation since they are based on a cohort that actually does receive MRI scans in the clinical setting. In addition, the proportion of patients with MCI converting to dementia did not differ significantly between patients with or without MRI. On the other hand, CSF analysis of AD biomarkers was *not* added as a covariate due to the risk of selection bias, because clinically, in patients with MCI, CSF examination is usually only carried out in patients suspected to have prodromal AD.  
Second, only one neuroradiologist (LC) rated the images. However, this rater has demonstrated high intra- and acceptable interrater reliability for the vaMTA in previous studies [28, 29]. Also, the MRI images were not carried out using the same protocol. However, the neuroradiologist (LC) was accustomed to those kinds of differences and took into account the risk of overestimating atrophy on T2 scans, and such differences are part of routine clinical practice. However, as 24 of the 35 MCI patients with T2 scans converted (69%), there is a risk of bias. In total, this further weakens the use of vaMTA as a predictor for MCI conversion.   
Third, there is a possibility that some patients had been misdiagnosed since the transition between MCI and AD is indefinite. However, the same doctors diagnosed the patients using the same criteria at baseline and follow-up and without knowing the baseline diagnosis when diagnosing the patients at follow-up.   
Finally, one cannot rule out that increasing the sample size would have changed the results.

To conclude, vaMTA was associated with MCI conversion in unadjusted model but did not reach significance in the adjusted model. VaMTA seemed positively associated with annual CDR-SB change in patients with MCI, but not in patients with AD. The CERAD delayed recall score was found to be a clinically useful predictor of both MCI conversion and of the degree of progression in both patients with MCI and mild AD.

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**Tables**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table 1. Patient characteristics. | | | | | | |
|  | MCI  n=94 | AD n=124 | p | MCI non-converters n=41 | MCI converters n=53 | p |
| Age, years | 68.6 (10.6) | 74.0 (7.2) | **<0.001a** | 63.5 (10.5) | 72.6 (8.9) | **<0.001a** |
| Female, n (%) | 46 (48.9) | 70 (56.5) | 0.271b | 19 (46.3) | 27 (50.9) | 0.658b |
| Education, years | 12.9 (3.4) | 11.4 (3.6) | **0.002a** | 13.4 (3.6) | 12.6 (3.3) | 0.251a |
| Duration of symptoms, years | 3.0 (3.0) | 3.3 (3.1) | 0.444a | 3.1 (3.6) | 2.9 (2.6) | 0.796a |
| MMSE score | 27.2 (2.4) | 22.1 (4.3) | **<0.001a** | 28.2 (1.9) | 26.3 (2.4) | **<0.001a** |
| CERAD delayed recall score | 3.5 (2.4) | 1.3 (1.7) | **<0.001a** | 5.4 (1.9) | 2.2 (1.7) | **<0.001a** |
| APOE-ɛ4 -carriers, n (%) | 47 (56.0) | 72 (62.9) | 0.320b | 14 (38.9) | 33 (68.8) | **0.006b** |
| vaMTA mean score | 1.5 (0.8) | 2.0 (1.0) | **<0.001a** | 1.1 (0.7) | 1.8 (0.8) | **<0.001a** |
| Hypertension, n (%) | 35 (37.2) | 53 (42.7) | 0.412b | 11 (26.8) | 24 (45.3) | 0.066b |
| Homocysteine, µmol/L | 13.4 (5.0) | 14.7 (4.9) | 0.090a | 12.1 (3.4) | 14.7 (5.9) | **0.024**a |
| eGFR (CPD), mL/min/1.73 m2 | 80.8 (15.7) | 75.9 (16.9) | **0.029a** | 85.6 (16.2) | 77.1 (14.4) | **0.008a** |
| Cornell score | 4.9 (4.6) | 5.4 (4.8) | 0.402a | 5.6 (4.0) | 4.3 (5.0) | 0.216a |
| CDR-SB at baseline | 1.79 (1.09) | 5.02 (1.64) | **<0.001a** | 1.40 (1.04) | 2.08 (1.05) | **0.002a** |
| CDR-SB at follow-up | 3.72 (3.45) | 9.14 (3.89) | **<0.001a** | 1.32 (1.22) | 5.58 (3.47) | **<0.001a** |
| CDR-SB annual change | 0.91 (1.55) | 2.14 (2.01) | **<0.001**a | -0.06 (0.65) | 1.67 (1.63) | **<0.001**a |
| a student’s t-test, b X2test  All continuous variables are expressed as mean (SD).  MCI=Mild cognitive impairment, AD=Alzheimer’s disease, MMSE=Mini-mental state examination, CERAD=Consortium to establish a registry for Alzheimer’s disease, vaMTA=visually assessed medial temporal lobe atrophy a.m. Scheltens, eGFR=estimated glomerular filtration rate, CDR-SB=Clinical dementia rating scale-sum of boxes. | | | | | | |

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| Table 2. Predictors of conversion from mild cognitive impairment to dementia during 24 months follow-up (logistic regression analysis for hierarchical data, n=71 with complete data). | | | | |
|
|  | Unadjusted | | Adjusteda | |
|  | OR (95% CI) | p | OR (95% CI) | p |
| Age | 1.13 (1.05; 1.21) | **0.002** | 1.05 (0.96; 1.15) | 0.279 |
| Female | 1.17 (0.41; 3.34) | 0.760 | 0.61 (0.11; 3.41) | 0.571 |
| Education | 0.98 (0.84; 1.16) | 0.843 |  |  |
| CERAD delayed recall | 0.39 (0.25; 0.60) | **<0.001** | 0.39 (0.23; 0.64) | **<0.001** |
| vaMTA mean | 6.41 (2.23; 18.39) | **0.001** | 3.58 (0.88; 14.59) | 0.075 |
| Cornell score | 0.98 (0.88; 1.10) | 0.736 |  |  |
| APOE-ɛ4 carrier | 2.46 (0.86; 7.09) | 0.094 | 6.25 (1.06; 36.79) | **0.043** |
| Hypertension | 1.78 (0.61; 5.19) | 0.284 |  |  |
| Follow-up time | 1.04 (0.88-1.23) | 0.636 |  |  |
| aModel reduced by Akaike's Information Criteria CERAD=Consortium to establish a registry for Alzheimer’s disease, vaMTA=visually assessed medial temporal lobe atrophy a.m. Scheltens | | | | |

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| Table 3. Factors associated with global cognitive and functional decline as measured by the annual change in CDR-SB in patients with mild cognitive impairment, and Alzheimer’s disease with mild degree of dementia (linear regression analysis). | | | | |
|  | Unadjusted | | Adjusteda | |
|  | Coefficient (SE) | p | Coefficient (SE) | p |
| Age | 0.06 (0.02) | **<0.001** | 0.04 (0.02) | **0.034** |
| Female | -0.03 (0.31) | 0.929 | -0.26 (0.29) | 0.376 |
| Education | -0.03 (0.05) | 0.563 |  |  |
| CERAD delayed recall1 | -0.27 (0.06) | **<0.001** | -0.18 (0.08) | **0.029** |
| Cornell score | -0.03 (0.03) | 0.327 |  |  |
| APOE-ɛ4 carrier | 0.38 (0.31) | 0.218 |  |  |
| Hypertension | 0.35 (0.31) | 0.253 |  |  |
| Follow-up time | -0.09 (0.05) | 0.055 |  |  |
| vaMTA mean | 0.64 (0.27)2 | **0.020** | 0.15 (0.30) | 0.607 |
| Diagnosis3 | 2.29 (0.66)2 | **0.001** | 1.45 (0.69) | **0.036** |
| MTA x diagnosis | -0.78 (0.34)2 | **0.020** | -0.51 (0.08) | 0.134 |
| aModel reduced with use of Akaike's Information Criteria  1An interaction between CERAD delayed recall and diagnosis was tested but was not significant neither in the unadjusted nor adjusted models and was omitted from table.  2Coefficient adjusted for the other two components of the interaction term  3MCI=0, AD=1  CERAD=Consortium to establish a registry for Alzheimer’s disease, vaMTA=visually assessed medial temporal lobe atrophy a.m. Scheltens, MCI=Mild cognitive impairment, AD=Alzheimer’s disease, CDR-SB=Clinical dementia rating scale-sum of boxes. | | | | |

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| Table 4. Predictors of group belonging in trajectory analysis, group 1 as the reference group. Nominal logistic regression analysis for hierarchical data. | | | | |
|  | Unadjusted | | Adjusteda | |
| OR (95% CI) | p | OR (95% CI) | p |
| *Group 2* |  |  |  |  |
| Age  Female | 1.09 (1.04; 1.14)  1.26 (0.62; 2.55) | **<0.001**  0.529 | 1.08 (1.01; 1.16)  0.87 (0.30; 2.46) | **0.020**  0.787 |
| Education  vaMTA mean  CERAD delayed recall  APOE-ɛ4 carrier  Cornell score  Follow-up time  Hypertension  Diagnosis1 | 0.94 (0.85; 1.04)  2.29 (1.46; 3.58)  0.63 (0.52; 0.77)  1.69 (0.82; 3.46)  1.08 (1.00; 1.17)  0.91 (0.82; 1.01)  1.22 (0.60; 2.51)  32.35 (11.12; 94.15) | 0.253  **<0.001**  **<0.001**  0.154  0.056  0.089  0.580  **<0.001** | 0.78 (0.61; 1.00)  1.15 (1.02; 1.29)  29.83 (8.93; 99.63) | 0.051  **0.021**  **<0.001** |
| *Group 3* |  |  |  |  |
| Age  Female | 1.12 (1.01; 1.25)  0.36 (0.06; 2.01) | **0.038**  0.243 | 1.11 (0.97; 1.27)  0.25 (0.04; 1.65) | 0.124  0.149 |
| Education  vaMTA mean  CERAD delayed recall  APOE-ɛ4 carrier  Cornell score  Follow-up time  Hypertension  Diagnosis1 | 0.83 (0.64; 1.07)  1.54 (0.61; 3.87)  0.49 (0.28; 0.86)  2.24 (0.40; 12.56)  0.97 (0.79; 1.20)  0.91 (0.71; 1.16)  1.21 (0.25; 5.97)  25.00 (3.82; 163.83) | 0.154  0.361  **0.013**  0.359  0.797  0.436  0.811  **0.001** | 0.61 (0.34; 1.08)  1.06 (0.85; 1.33)  20.70 (2.68; 159.98) | 0.087  0.600  **0.004** |
| *Group 4* |  |  |  |  |
| Age  Female | 1.11 (1.05; 1.18)  1.16 (0.51; 2.65) | **<0.001**  0.724 | 1.12 (1.03; 1.22)  0.72 (0.21; 2.49) | **0.010**  0.598 |
| Education  vaMTA mean  CERAD delayed recall  APOE-ɛ4 carrier Cornell score  Follow-up time  Hypertension  Diagnosis1 | 0.92 (0.81; 1.03)  2.59 (1.56; 4.30)  0.50 (0.37; 0.66)  1.43 (0.62; 3.31)  1.07 (0.97; 1.17)  0.86 (0.75; 0.98)  1.39 (0.60; 3.19)  185.00 (34.00; 1006.63) | 0.147  **<0.001**  **<0.001**  0.397  0.167  **0.022**  0.440  **<0.001** | 0.65 (0.46; 0.91)  1.15 (1.00; 1.32)  163.60 (26.30; 1017.54) | **0.013**  0.050  **<0.001** |
| aModel reduced with use of Akaike's Information Criteria  1MCI=0, AD=1  CERAD=Consortium to establish a registry for Alzheimer’s disease, vaMTA=visually assessed medial temporal lobe atrophy a.m. Scheltens, MCI=Mild cognitive impairment, AD=Alzheimer’s disease | | | | |

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| Supplemental table 1. Descriptives by groups detected in trajectory analysis. | | | | | |
|  | Group 1 | Group 2 | Group 3 | Group 4 | p |
| Diagnosis  MCI, n (%)  AD, n (%)  Age  Min, max  Mean (SD)  Gender  Male, n (%)  Female, n (%)  Education  Min, max  Mean (SD)  MMSE  Min, max  Mean (SD)  CERAD delayed recall  Min, max  Mean (SD)  Follow-up time  Min, max  Mean (SD)  vaMTA mean  Min, max  Mean (SD)  APOE-ɛ4 carrier  Non-carrier, n (%)  Carrier, n (%)  Cornell score  Min, max  Mean (SD)  Hypertension  No, n (%)  Yes, n (%)  CDR-SB annual change  Min, max  Mean (SD) | 67 (93.1)  5 (6.9)  26, 90  66.8 (10.7)  36 (50.0)  36 (50.0)  7, 20  13.0 (3.4)  17, 30  27.4 (2.6)  0, 9  4.0 (2.4)  16, 35  25.0 (3.5)  0, 4  1.4 (0.8)  32 (48.5)  34 (51.5)  0, 16  4.4 (4.1)  48 (66.7)  24 (33.3)  -1.7, 2.1  0.3 (0.7) | 21 (24.4)  65 (75.6)  56, 88  73.7 (7.1)  38 (44.2)  48 (55.8)  7, 20  11.9 (3.7)  13, 30  24.1 (3.5)  0, 9  1.7 (1.8)  17, 33  24.0 (3.1)  0, 4  2.0 (0.9)  28 (34.6)  53 (65.4)  0, 23  5.7 (5.0)  51 (59.3)  35 (40.7)  -1.2, 4.9  1.1 (1.1) | 2 (25.0)  6 (75.0)  65, 90  75.3 (8.1)  5 (62.5)  3 (37.5)  7, 17  10.6 (3.4)  11, 22  19.0 (3.9)  0, 3  1.0 (1.3)  18, 33  23.8 (4.3)  0.5, 3  1.8 (0.9)  2 (25.0)  6 (75.0)  0, 12  3.6 (4.0)  4 (50.0)  4 (50.0)  5.5, 9.3  6.8 (1.2) | 4 (7.7)  48 (92.3)  56, 89  74.5 (7.7)  23 (44.2)  29 (55.8)  7, 20  11.3 (3.4)  7, 29  21.3 (4.8)  0, 5  1.0 (1.6)  18, 34  23.8 (3.2)  0.5, 4  2.1 (1.0)  18 (40.0)  27 (60.0)  0, 27  5.5 (5.1)  27 (51.9)  25 (48.1)  0.7, 7.0  3.5 (1.4) | **<0.001**1  **<0.001**2  0.6911  **0.026**2  **<0.001**2  **<0.001**2  0.5372  **<0.001**2  0.2931  0.2902  0.3801  **<0.0012** |
| 1 χ2-test; 2 ANOVA  MCI=Mild cognitive impairment, AD=Alzheimer’s disease, MMSE=Mini-mental state examination, CERAD=Consortium to establish a register for Alzheimer’s disease, vaMTA=visually assessed medial temporal atrophy a.m. Scheltens, CDR-SB=Clinical dementia rating scale-sum of boxes. | | | | | |

Fig. 1. Flow chart  
Fig. 2. Association between MTA mean at baseline and annual change in CDR, by diagnosis, unadjusted result.  
Fig. 3. Trajectory analysis, showing four well-defined groups with different progression slopes.

Figure

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*Figure 2*

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Figure

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