Trajectories of depressive symptoms and their relationship to the progression of dementia

Maria Lage Barca, MD, PhD [1, 2], Karin Persson, MD [1, 2], Rannveig Eldholm, MD [3], Jūratė Šaltytė Benth, PhD [5, 6], Hege Kersten, PhD, Associate professor [1, 7, 8], Anne-Brita Knapskog, MD, PhD [2], Ingvild Saltvedt, MD, PhD [3, 4], Geir Selbaek, MD, PhD, Professor [1, 9], Knut Engedal, MD, PhD, Professor emeritus [1, 2]

[1] Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Norway

[2] Department of Geriatric Medicine, Oslo University Hospital, Norway

[3] Department of Neuromedicine and Movement science, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[4] Geriatric Department, St. Olav Hospital, University Hospital of Trondheim, Norway

[5] Institute of Clinical Medicine, Campus Ahus, University of Oslo, Norway

[6] HØKH, Research Centre, Akershus University Hospital, Norway

[7] Department of Pharmaceutical Bioscience, School of Pharmacy, University of Oslo, Norway

[8] Telemark Hospital Trust, Skien, Norway

[9] Research Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad, Norway

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Corresponding author: Maria Lage Barca, Norwegian National Advisory Unit on Ageing and Health Department of Geriatric Medicine, Oslo University Hospital, Ullevål, 20, 4. etg, 0450 Oslo, Norway.

Telephone: (+47) 9743-6610

E-mail: maria.barca@aldringoghelse.no

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Abstract

Background: The relationship between progression of Alzheimer's disease and depression and its underlying mechanisms has scarcely been studied.

Methods: A sample of 282 outpatients with Alzheimer's disease (AD; 105 with amnestic AD and 177 with Alzheimer's dementia) from Norway were followed up for an average of two years. Assessment included Cornell Scale for Depression in Dementia and Clinical Dementia Rating Scale (CDR) at baseline and follow-up to examine the relationship between AD and depression. Additionally, MRI of the brain, CSF dementia biomarkers and APOE status were assessed at baseline. Progression of dementia was defined as the difference between CDR sum of boxes at follow-up and baseline (CDR-SB change). Trajectories of depressive symptoms on the Cornell Scale were identified using growth mixture modeling. Differences between the trajectories in regard to patients' characteristics were investigated.

Results: Three distinct trajectories of depressive symptoms were identified: 231 (82.8%) of the patients had stable low-average scores on the Cornell Scale (Class 1); 11 (3.9%) had high and decreasing scores (Class 2); and 37 (13.3%) had moderate and increasing scores (Class 3). All classes had average probabilities over 80%, and confidence intervals were non-overlapping. The only significant characteristic associated with membership in class 3 was CDR-SB change.

Limitations: Not all patients screened for participation were included in the study, but the included and non-included patients did not differ significantly. Some patients with amnestic MCI might have been misdiagnosed.

Conclusion: A more rapid progression of dementia was found in a group of patients with increasing depressive symptoms.

Keywords: depression, trajectory, dementia, mild cognitive impairment, prognosis, memory clinic

Introduction

The number of individuals with Alzheimer's disease (AD) is increasing worldwide. In 2015, 46.8 million people were identified as having AD, and it is estimated that 131.5 million will have the disease by 2050 (Alzheimer's disease international, 2015). A curative treatment for AD is still lacking. Therefore, efforts are being made to develop strategies to prevent the disease or to delay its progression. Several modifiable risk factors such as depression, diabetes and hypertension have been reported for AD dementia (Deckers et al., 2015, Kivipelto et al., 2006, Norton et al., 2014, Ngandu et al., 2015).

The literature regarding factors influencing the progression of AD is scarce. The identification of such factors, especially potentially modifiable factors, would be of crucial importance. The treatment of such conditions may be seen as a form of secondary prevention by slowing the progression of the disease and diminishing the negative consequences of AD. In this paper, we will focus on depression and its relationship to the progression of AD.

The relationship between depression and dementia in AD is complex. Depression has been reported as a risk factor for all types of dementia, including AD (Saczynski et al., 2010, Byers and Yaffe, 2011, Ownby et al., 2006, Diniz et al., 2013, Deckers et al., 2015). In addition, several authors have pointed to the potential of preventing dementia by treating depression (Lyketsos et al., 2011, Kessing, 2012). Depression can be a prodromal symptom of dementia, especially when depression has its onset late in life and appears close to the onset of dementia (Li et al., 2011, Bennett and Thomas, 2014, Masters et al., 2015). It is also well known that depression can be a consequence of dementia (Lyketsos and Olin, 2002, Olin et al., 2002, Barca et al., 2010).

The findings in regard to whether depression accelerates the progression of AD are controversial. One population study found that depression did not accelerate the progression

of dementia among patients with AD (Leoutsakos et al., 2015), whereas other studies reported the opposite (Rapp et al., 2011, Wilson et al., 2002). However, pathophysiological mechanisms underlying depressive symptoms in AD and their roles in the progression of the disease have not yet been investigated.

Depression and AD may have common etiological mechanisms. Depression may cause increased circulation of glucocorticoids, which, in turn, could lead to hippocampal atrophy (Byers and Yaffe, 2011). One study reported that patients with depression in AD had more medial temporal lobe atrophy (MTA) than patients with AD without depression (Dhikav et al., 2014), and a post-mortem study revealed that AD patients with a history of depression had more neuritic plaques and neurofibrillary tangles in the hippocampus than those without a history of depression (Rapp et al., 2006). Another similarity is that cardiovascular diseases are risk factors for both depression and AD (Almeida et al., 2007, Kivipelto et al., 2006). Moreover, neuroinflammation has been reported in both depression and dementia, with increased levels of similar pro-inflammatory cytokines (Hong and Kim, 2016). Therefore, depression could pose an additive effect in AD. Indeed, it has been shown that depression (Modrego and Ferrandez, 2004) and, especially, increasing depressive symptoms over time (Kaup et al., 2016) are risk factors for all-cause dementia. However, whether increasing depressive symptoms over time in AD accelerate cognitive decline or the progression of dementia has not yet been investigated.

This is an exploratory study that aims to investigate the different trajectories of depressive symptoms among patients with AD and the relationship between the progression of AD and different trajectories.

Methods

Participants

The Prognosis of Alzheimer's disease and Resource use (PADR) study is a longitudinal, observational study among Norwegian patients from two memory clinics and one geriatric outpatient unit, with one assessment at the time of the patients' first visit to the clinics and one follow-up assessment after 16–37 months. Inclusion criteria were: having a diagnosis of MCI or dementia, having the capacity to provide consent at baseline, having an available proxy, being fluent in the Norwegian language, living in proximity to the center (close enough to be reassessed) and having no serious comorbid diseases at baseline.

Of 555 patients screened, 198 were not included at follow-up due to various reasons, resulting in 357 patients being assessed after an average of two years. Patients with diagnoses other than AD, such as non-amnestic mild cognitive impairment and other types of dementia (N=75) were excluded from the present study, resulting in 282 patients with Alzheimer's disease: 177 with dementia due to AD and 105 with prodromal AD defined as amnestic MCI, (see "Diagnoses" for details). Patients who completed follow-up had completed more years of education compared to those who did not complete follow-up. Otherwise, there were no differences regarding age, gender, Cornell score, CDR sum of boxes, and MMSE score.

Figure 1 here

Assessments

The baseline assessments of the patients were performed by physicians at the outpatient clinics and included a clinical history from patients and their caregivers, neuropsychological tests, physical and cognitive examinations, blood analyses (including analysis of APO E status among 252 patients) and, usually, structural brain imaging with MRI or CT. In some cases, SPECT and PET were also performed. Cerebrospinal fluid (CSF) was drawn from 110 of the 282 patients for the analyses of amyloid-β (Aβ), total tau (T-tau) and phospho tau (P-tau). Nurses interviewed the caregivers with structured instruments to evaluate activities of

daily living and neuropsychiatric symptoms including depression. The follow-up assessment was conducted by research physicians using a protocol similar to that at baseline. Additionally, saliva was collected, three times during the same day.

The demographic characteristics included were age, gender and level of education. Cardiovascular diseases were dichotomized based on the history of cardiovascular disease at baseline. Anatomical Therapeutic Chemical (ATC) codes were registered for all drugs. Antidepressants were identified by the pharmacological subgroup N06A and dichotomized for any antidepressant used at baseline.

The Cornell Scale for Depression in Dementia (CSDD) was used to rate the severity of depressive symptoms (Alexopoulos et al., 1988). The scale has been validated in Norwegian memory clinics, and a cut-off ≥6 was found for depression (Knapskog et al., 2011). Each of the 19 items is rated from 0 (no symptom) to 2 (severe symptom), giving a sum score of 0–38, with higher scores indicating more severe depression. Several items in the Cornell Scale were scored as "not possible to evaluate". Such items would affect the sum score, making it artificially low. Therefore, the average score was used as a continuous variable at baseline and at follow-up.

The Physical Self-Maintenance Scale was used to assess the patients' abilities to perform personal activities of daily living (PADL). This scale has six items, and each item can be scored between 1 and 5. The Instrumental Activities of Daily Living Scale (IADL) was used to evaluate instrumental activities of daily living. This scale has eight items, and each item can be scored between 0 and 3–5; a higher score denotes greater impairment (Lawton and Brody, 1969). Both scales were summarized to evaluate activities of daily living (ADL) as one continuous variable.

The Mini-Mental State Examination (MMSE) was applied to rate global cognitive functioning. The score on the MMSE varies between 0 and 30; a higher score denotes better cognition (Folstein et al., 1975).

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word delayed recall test was performed, with scores between 0 and 10; a higher score denotes better delayed recall (Fillenbaum, 2008).

We used the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982) to assess the severity of dementia. This instrument includes six domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. We calculated the CDR sum of boxes (CDR-SB), where 0 indicates no impairment and 18 the most severe impairment. The CDR-SB has been proposed as the primary outcome measure for clinical trials in early AD (Cedarbaum et al., 2013). All study researchers underwent online training and fulfilled the requirements for certification. A difference between CDR-SB at follow-up and CDR-SB at baseline was used to assess progression.

Magnetic resonance imaging (MRI) was evaluated visually for medial temporal lobe atrophy (MTA) according to the Scheltens' Scale by an experienced neuroradiologist. This scale varies between 0 and 4, where a higher score indicates more atrophy (Scheltens et al., 1992). We added the scores for the right and left sides and used this measurement as one continuous variable. MRI was also evaluated regarding white matter hyperintensities (WMH) with the Fazekas Scale. This scale evaluates white matter lesions and the score varies between 0 and 3; higher scores indicate more hyperintensities in the white matter. It was also used as a continuous variable (Fazekas et al., 1987). At baseline, 242 MRIs were evaluated. However, 17 of these were performed more than six months before or after the baseline evaluation and were, therefore, excluded from the analysis, resulting in 225 MRIs.

APOE typing was performed using the Illumina Infinium OmniExpress v1.1 chip at deCODE Genetics, Reykjavik, Iceland. APOE ε4 status was dichotomized according to the presence or absence of one or two APOE ε4 allele(s). Saliva was collected at three time points during the same day (morning, 7–9am; afternoon, 12–2pm; and evening, 9–11pm) according to recommended procedures using Salivette (Sarstedt®) and analyzed for concentration of cortisol using first-generation methodology. In the present study, the values for cortisol were used as a continuous variable.

Diagnoses

Dementia diagnoses were made by one or two experienced physicians (details in the next paragraph) according to the ICD-10 criteria for research. For dementia due to AD, we used the NINCDS-ADRDA criteria (McKhann et al., 1984). The Winblad criteria were used for MCI (Winblad et al., 2004). When diagnosing the patients at baseline, all available data from the first visit, such as anamnesis from both the patient and a caregiver, results from a neuropsychological test battery, physical examination, blood tests and results from supplementary examinations such as MRI of the brain, brain SPECT/PET and the CSF biomarkers Aβ, T-tau and P-tau, were used. Patients with amnestic MCI (aMCI), defined as MCI patients with memory complaints as expressed by the patient and/or caregiver and a score below -1.5 SD on at least one memory test, with no other obvious etiology for cognitive impairment, were regarded as Alzheimer's disease patients. Additionally, CSF biomarkers and clinical MRI reports were used when sub-categorizing the MCI patients.

In 51 patients randomly selected from baseline, an inter-rater reliability analysis between the diagnoses made by two of the doctors in the project (MLB and KP) was performed. The result showed acceptable inter-rater agreement for the MCI diagnosis (kappa=0.66) and for dementia due to AD (kappa=0.73 [early onset] or 0.85 [late onset]). Therefore, in this memory

clinic, all AD patients were diagnosed by one skilled doctor. For all other patients (N=130), the diagnosis was discussed in consensus with a skilled professor (KE). Patients from the other two clinics were diagnosed by two doctors with significant amounts of experience in dementia work-up in consensus. At follow-up, all patients were diagnosed by two experienced doctors in consensus.

Statistical analysis

Missing values on PADL, IADL and Cornell items were imputed by drawing a random number from an empirical distribution generated for each relevant item. The imputation was performed only for patients with fewer than half of the values missing on the scale.

Differences between groups were analyzed with Mann-Whitney or Kruskal-Wallis tests for continuous and χ^2- test for categorical variables. A growth mixture model was estimated based on the mean Cornell score, with an attempt to identify unobserved classes of patients, each following a distinct trajectory. Due to still-missing values ("not possible to evaluate") on several Cornell items after imputation, the mean score was used instead of the sum score. Missing values would produce artificially low sum scores, while this problem is avoided by averaging the scores of existing items. Akaike's Information Criterion (AIC) was applied for identifying trajectories. In addition, the average class probabilities were expected to be larger than 0.7 and to have 95% confidence intervals (CI) for non-overlapping trajectories. To determine patient characteristics that could describe the trajectory classes, first, a number of bivariate analyses were carried out. Then the multivariate regression model with class membership as a dependent variable was estimated and reduced by applying AIC. All analyses were performed by SPSS v22 and STATA v14.

Ethical issues

The study was approved by the Regional Committee of Medical Research Ethics of the South-East Norway Regional Health Authority (REC South-East number 2011/531). All patients were informed and signed an informed consent.

Results

Three patients had missing on the Cornell Scale on both baseline and follow-up and had to be excluded from the analyses. Characteristics of the 279 patients and differences between the two AD groups (with and without dementia) are shown in Table 1. Patients with aMCI were younger, had higher levels of education, higher MMSE and lower CDR-SB, ADL, Cornell and MTA scores, as well as higher Aβ than those with AD. The prevalence of depression at baseline was 36.3% and 32.5% at follow-up, according to the Cornell Scale applying the Norwegian cut-off for memory clinics (score of 6 and above).

Table 1 here

Three distinct trajectories of depressive symptoms on the Cornell Scale were identified according to a growth mixture model (Figure 2). In all, 231 patients (82.8%) had stable low scores on the Cornell (Class 1); 11 patients (3.9%) had high and decreasing scores (Class 2); and 37 patients (13.3%) had moderate and increasing scores on the Cornell Scale (Class 3). All classes had average probabilities above 0.80 (Table 2) and confidence intervals were non-overlapping, clearly indicating distinct groups of patients.

Figure 2 here

Table 2 here

To explore how the patients of the different trajectories differed, we compared patient characteristics at baseline across classes of trajectories (Table 3). Compared to class 1, patients in class 2 had higher CDR-SB and used more antidepressants at baseline. Compared to class 1, patients in class 3 had lower Aβ, and a higher proportion used antidepressants at baseline; they also had a more rapid dementia progression according to CDR change. Class 2 and class 3 had no statistically significant differences in any characteristic.

Table 3 here

Class 2 was, unfortunately, too small to be included in the multivariate analysis. Therefore, we continued the analyses comparing class 3 with class 1 using logistic regression. First, unadjusted analyses were performed with class 3 versus class 1 as the dependent variable, and characteristics described in Table 3 were used as independent variables. However, there were too few patients with CSF biomarkers and cortisol, so we had to exclude these variables from further analyses to avoid bias. Instead, we added diagnosis (aMCI vs. dementia) as an independent variable, since we had found that patients with aMCI had higher Aβ levels. Table 4 shows the unadjusted odds ratios. The only significant characteristic that was associated with class membership in group 3 compared to class membership in group 1 in the multivariate model was the CDR change, indicating that the a more rapid progression as measured by CDR between baseline and follow-up was associated with increasing depressive symptoms as measured by the Cornell Scale.

Table 4 here

Discussion

The main aim of the present study was to investigate the underlying trajectories of depressive symptoms among patients with AD. We found three distinct trajectories of depressive symptoms as measured by the Cornell Scale. The largest class of patients had minimal

changes in the Cornell score; the second-largest class had moderate symptoms at baseline that increased; and the smallest class had severe symptoms at baseline that decreased.

To the best of our knowledge, this is the first study that has investigated trajectories of depressive symptoms among patients with AD in a clinical sample. Two recently published studies have evaluated trajectories of depressive symptoms among community-dwelling older adults. One of these studies evaluated elderly persons without dementia according to the Center for Epidemiologic Studies Depression Scale Short Form with 10 items (CES-D) and found three trajectories, consistently minimal symptoms (62.0%), moderate and increasing symptoms over time (32.2%), and high and increasing symptoms over time (5.8%) (Kaup et al., 2016). Another study of elderly persons, including both persons with and without cognitive impairment, found five trajectories of depressive symptoms using the complete CES-D scale with 20 items: rarely depressed (60.5%); low-grade, decreasing symptoms (18.5%); low-grade, increasing symptoms (9.6%); moderate-grade symptoms (7.4%); and consistently higher-grade symptoms (4.0%) (Graziane et al., 2016). Our findings are in line with the trajectories found by Kaup et al., that is, the largest group with constantly minimal depressive symptoms, the second-largest with moderate and increasing symptoms, and a third group with more severe symptoms that increased over time. In contrast, we found a small group with severe depressive symptoms that decreased over time. The reduction of depressive symptoms could not be explained by increased use of antidepressants or by differences in APOE ε4 status between the classes of trajectories. We suggest that the use of various depression scales may explain the differences between studies. The population studies used the CES-D scale in two different forms. The present study used the CSDD, which was originally developed to measure depressive symptoms among patients with dementia but is also validated for use among patients without dementia.

Differences between groups were investigated. Patients in group 2, with decreasing depressive symptoms, had higher CDR-SB and used more often antidepressants at baseline compared to patients in group 1. This can be regarded as an indirect sign that antidepressants were effective. Patients in group 3, that had moderate depressive symptoms that increased, also used more often antidepressants compared to patients in group 1. This is surprising, especially due to the finding that antidepressants were associated with decreasing depressive symptoms among patients in group 2. However, patients in group 3 had lower levels of Amyloid β, which might indicate more brain pathology. It is known that antidepressants have poorer effect among patients with Alzheimer's dementia than among elders without dementia (Bains et al., 2006, Thompson et al., 2007, Leong, 2014). However, there were no differences between group 2 and 3 regarding symptom severity of dementia as measured by the CDR-SB. Furthermore, only CDR-SB change was significant in the adjusted analyses. Therefore, we assume that the progression of dementia cannot be avoided in spite of antidepressant use.

We found that greater progression of AD is associated with increasing depressive symptoms, adjusted for several factors, such as demographic characteristics, cardiovascular comorbidity, APOE ε4 status and MRI findings such as atrophy of medial temporal lobe according to Scheltens' Scale and white matter hyperintensities according to Fazekas' Scale, antidepressant use and dementia vs MCI diagnosis.

Controversial findings have been reported in regard to whether depression accelerates the progression of AD. Several studies have found that depression accelerates dementia progression (Wilson et al., 2002, Rapp et al., 2011), but another study that adjusted the analyses for a number of factors did not (Leoutsakos et al., 2015). The study by Kaup et al. found that the high and increasing trajectory of depressive symptoms increased the risk of incident dementia compared to the consistently minimal trajectory adjusted for several factors, including demographic characteristics, cardiovascular comorbidities and APOE ε4

(Kaup et al., 2016). Another previously mentioned study found an association between increasing depressive symptoms and poor cognition (Graziane et al., 2016). That study investigated associations between depression trajectories and trajectories of a number of cognitive domains and found that the low-grade increasing depression trajectory class, and not the high-grade class, was associated with persistently poor cognitive functioning, a finding different compared to the present study. Several mechanisms have been hypothesized for why depression would be associated with faster or greater progression of Alzheimer's disease. First, it has been shown that chronic depression leads to hippocampal atrophy (Sheline et al., 2003). Moreover, cardiovascular factors are risk factors for both depression (Almeida et al., 2007) and dementia (Kivipelto et al., 2006), and it is possible that these factors would booster the progression of Alzheimer's disease in patients with comorbid depression. We investigated differences between the trajectory classes with increasing depressive symptoms and with minimal depressive symptoms. For the reasons listed above, we would expect that the group with increasing depressive symptoms would have more medial temporal atrophy, more white matter hyperintensities and more cardiovascular diseases. However, this was not the case. One possible explanation for why we did not find such associations is that these patients had moderate depressive symptoms at baseline. It could be that they did not have these brain lesions as mentioned by other authors (Sheline et al., 2003) because they did not have severe enough depression to cause these alterations in the brain. It has been argued that one single measurement of depression is simply a snapshot and does not illustrate the whole process (Graziane et al., 2016). Some persons might be in a phase marked by the worsening of the depression and others in an ameliorating phase, as also shown by our results. Another possibility is that other brain regions might be involved in increasing depressive symptoms in our sample, such as the frontal lobe, as shown in another cohort (Soennesyn et al., 2012). Some studies have shown that patients with Alzheimer's disease and depression do not

present more Alzheimer's pathology as measured by CSF markers (Auning et al., 2015, Diniz et al., 2014).

Another possible explanation for our finding is that patients with faster dementia progression react with more depressive symptoms. There might be two mechanisms in this case: that faster progression leads to depression through biological or psychological mechanisms. Faster progression of dementia could lead to more depressive symptoms because of brain damages that could lead to organic depression through frontolimbic and frontostriatal pathways. Depression could also occur as a psychological reaction to greater impairments. It has been shown that awareness of the disease is associated with depression (Migliorelli et al., 1995). Finally, there is the possibility that depression may have caused cognitive impairment.

This study has some limitations. First, we have not included all the patients screened for inclusion, but the patients included and not included did not differ significantly. Also, the sample size is small compared to large population cohorts. The external validity for patients with MCI and dementia in the community is also limited, since it is a selective sample from a memory clinic. Another limitation is that some patients might have been misdiagnosed. We wanted to include all the patients from the spectrum of Alzheimer's disease (MCI and dementia stages), but some of the patients with MCI might have been classified with Alzheimer's disease without having it. However, 67 (63.8%) patients with aMCI at baseline progressed to dementia after the period of two years. Another limitation is that, since it is an observational study rather than an intervention study, we are not able to assure that the improvement of depressive symptoms was due to antidepressant treatment. The strength of our study is that is has been conducted in a clinical setting using valid scales and advanced diagnostic measurements.

Conclusion

In conclusion, we have found three trajectories of depressive symptoms. To the best of our knowledge, this is the first study to investigate trajectories of depressive symptoms in a clinical sample. Our findings are comparable to trajectories of depressive symptoms found in population studies. We also found that more rapid progression in dementia is associated with the moderate and increasing depressive symptoms trajectory.

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Conflicts of interest

None

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Figure 1. Flow-chart

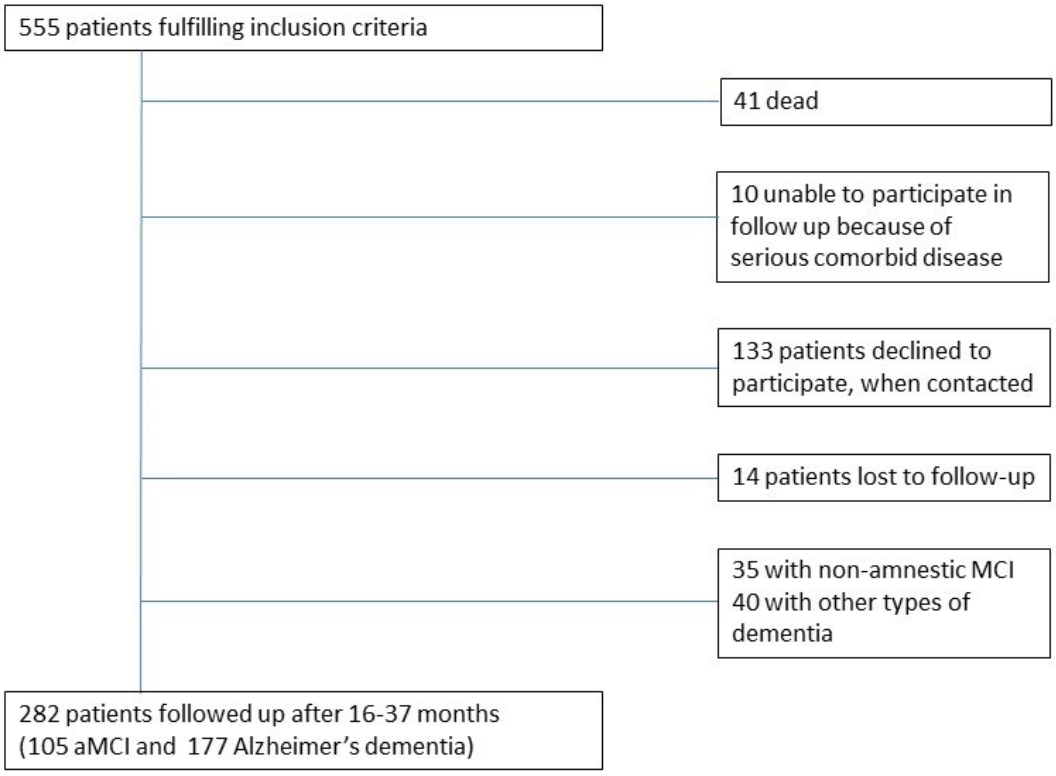

Table 1. Patients' characteristics at baseline				
	All (N=282)	**amnestic MCI (n=105)**	**Alzheimer's dementia (n=177)**	**p-value**
Age, n=282, mean (SD)	73.2 (8.8)	70.7 (10.1)	74.7 (7.6)	0.002[1]
Women, n=282, n (%)	152 (53.9)	50 (47.6)	102 (57.6)	0.103[2]
Education, years, n=282, mean (SD)	11.7 (3.6)	12.7 (3.5)	11.1 (3.5)	<0.001[1]
MMSE, n=280, mean (SD)	23.7 (4.4)	26.7 (2.5)	22.0 (4.3)	<0.001[1]
CDR-SB, n=282, mean (SD)	4.3 (2.8)	2.1 (1.3)	5.6 (2.5)	<0.001[1]
ADL, n=273, mean (SD)	18.4 (5.6)	15.8 (2.9)	20.2 (6.4)	<0.001[1]
Cornell score, n=259, median (range)	**4.0 (0-27)**	**3.0 (0-18)**	**5.0 (0-27)**	**0.008[1]**
Cardiovascular diseases, n=282, yes (%)	173 (61.3)	60 (57.1)	113 (63.8)	0.264[2]
APOE ε4 carrier, n=252, yes, n (%)	149 (52.8)	51 (55.4)	98 (61.3)	0.366[2]
MTA, n=212, median (range)	**4.0 (0-8)**	**3.0 (0-7)**	**4.0 (0-8)**	**<0.001[1]**
WMH n=215, median (range)	**2.0 (0-3)**	**2.0 (0-3)**	**2.0 (0-3)**	**0.213[1]**
Amyloid β, n=110, mean (SD)	595.4 (263.8)	752.7 (315.5)	518.9 (195.2)	<0.001[1]
Total tau, n=110, mean (SD)	663.9 (321.8)	611.3 (294.3)	689.5 (333.3)	0.261[1]
Phospho tau, n=110, mean (SD)	82.9 (33.4)	76.0 (29.2)	86.3 (35.0)	0.161[1]
Cortisol morning, n=182, mean (SD)	20.6 (28.3)	24.3 (38.7)	18.0 (17.5)	0.170[1]
Cortisol afternoon, n=187, mean (SD)	10.6 (17.2)	8.6 (8.3)	11.8 (21.2)	0.112[1]
Cortisol evening, n=181, mean (SD)	8.1 (22.4)	6.4 (7.5)	9.3 (28.7)	0.837[1]
Antidepressant, n=282, yes, n (%)	31 (11)	11 (10.5)	20 (11.3)	0.861[2]

[1] Mann-Whitney test

[2] χ^2-test

Figure 2. Trajectories analysis of depressive symptoms by the Cornell scale for depression

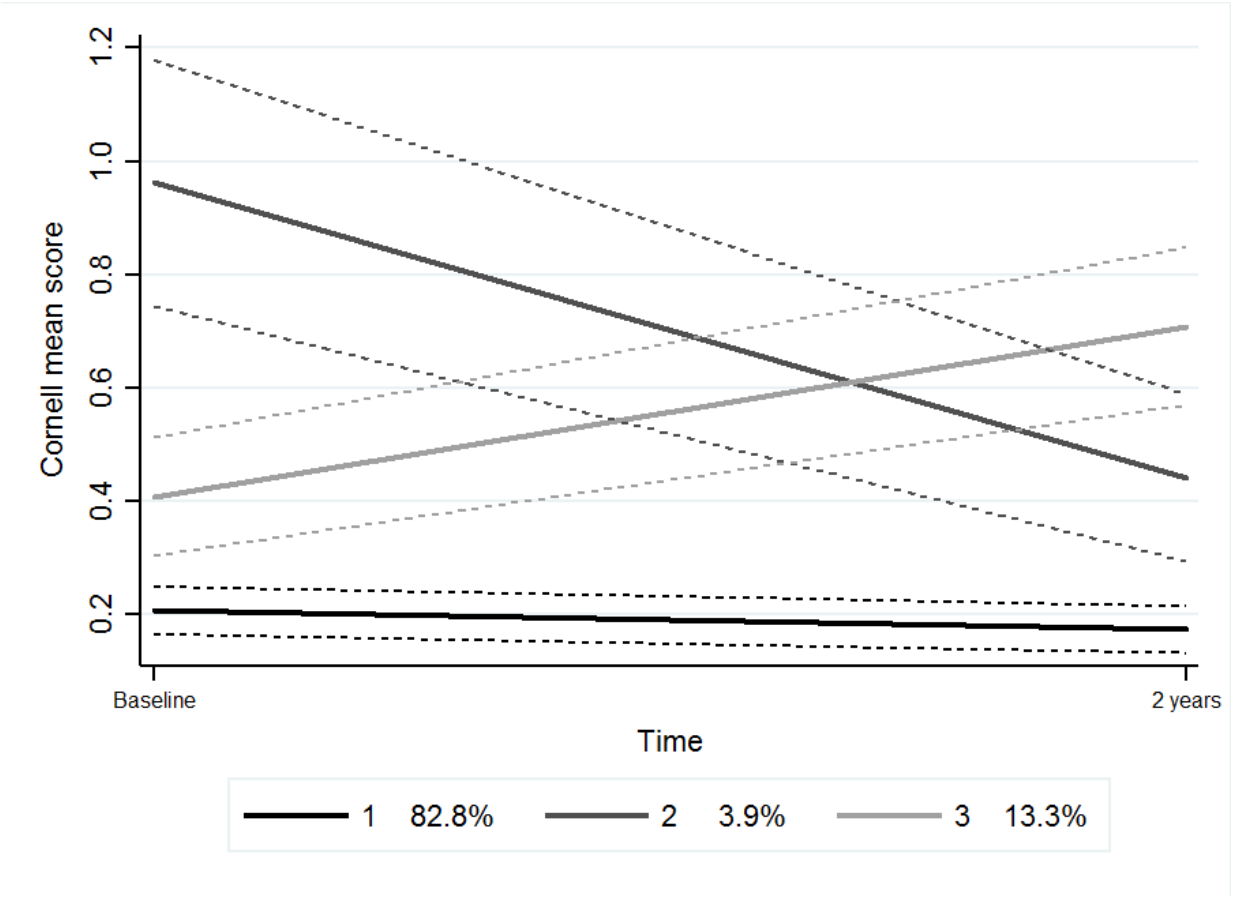

Table 2. Trajectories analysis of depressive symptoms by the Cornell scale for depression						
Variable	Class 1 (N=231)		Class 2 (N=11)		Class 3 (N=37)	
	Regr.coeff. (SE)	p-value	Regr.coeff. (SE)	p-value	Regr.coeff. (SE)	p-value
Intercept	0.23 (0.03)	<0.001	1.48 (0.23)	<0.001	0.10 (0.13)	0.421
Time	-0.04 (0.02)	0.039	-0.52 (0.13)	<0.001	0.30 (0.09)	0.001
Av. prob.	0.96		0.89		0.81	

Table 3. Unadjusted differences between trajectories groups							
	Class 1	**Class 2**	**Class 3**	**p-value**	**C1 vs C2**	**C1 vs C3**	**C2 vs C3**
Age, n=279, mean (SD)	73.5 (8.7)	66.8 (11.3)	73.1 (7.9)	0.147[1]	0.054[3]	0.703[3]	0.105[3]
Women, n=279, n (%)	125 (54.1)	7 (63.6)	18 (48.6)	0.660[2]	0.535[2]	0.536[2]	0.382[2]
MMSE, n=277, mean (SD)	23.8 (4.4)	22.3 (6.3)	23.4 (3.8)	0.613[1]	0.533[3]	0.417[3]	0.860[3]
CDR-SB, n=279, mean (SD)	4.2 (2.8)	6.0 (2.1)	4.5 (2.3)	0.022[2]	**0.010**[2]	0.258[2]	0.056[2]
CDR change, n=279, mean (SD)	2.9 (3.4)	3.5 (3.9)	4.8 (4.2)	0.020[1]	0.458[3]	**0.006**[3]	0.418[3]
ADL, n=257, mean (SD)	18.2 (5.7)	21.6 (4.2)	19.6 (5.5)	0.066[1]	0.067[3]	0.114[3]	0.383[3]
Cardiovascular diseases, n=279, yes, n (%)	143 (61.9)	9 (81.8)	20 (54.1)	0.246[2]	0.182[2]	0.364[2]	0.098[2]
Apo E ε4 carrier, n=249, yes, n (%)	122 (59.5)	5 (55.6)	20 (57.1)	0.944[2]	0.813[2]	0.792[2]	0.932[2]
MTA, n=231, mean (SD)	3.7 (1.9)	4.9 (2.3)	3.7 (1.7)	0.373[1]	0.172[3]	0.774[3]	0.186[3]
WMH, n= 240, mean (SD)	2.0 (0.9)	1.9 (0.8)	2.0 (0.9)	0.964[1]	0.791[3]	0.949[3]	0.821[3]
Amyloid β, n=110, mean, (SD)	605 (257)	807 (0)	504 (307)	0.049[1]	0.211[3]	**0.033**[3]	0.264[3]
Total tau, n=110, mean, (SD)	680 (325)	230 (0)	575 (278)	0.174[1]	0.116[3]	0.299[3]	0.172[3]
Phospho tau, n=110, mean, (SD)	85.0 (34.0)	34.0 (0)	71.4 (25.0)	0.114[1]	0.100[3]	0.200[3]	0.107[3]
Cortisol morning, n=180, mean (SD)	20.1 (28.5)	18.7 (9.9)	26.1 (31.5)	0.510[1]	0.646[3]	0.277[3]	0.865[3]
Cortisol afternoon, n=184, mean (SD)	10.2 (17.8)	10.5 (4.8)	13.6 (15.3)	0.094[1]	0.139[3]	0.090[3]	1.000[3]
Cortisol evening, n= 179, mean (SD)	7.2 (19.8)	9.6 (6.5)	16.8 (40.4)	0.056[1]	0.077[3]	0.085[3]	0.551[3]
Antidepressant, n=279, yes, n (%)	18 (7.8)	3 (27.3)	7 (18.9)	0.017[2]	**0.025**[2]	**0.031**[2]	0.549[2]

[1] Kruskall-Wallis test [2] χ^2-test [3] Mann-Whitney test

Table 4. Logistic regression for class membership in class 3 (moderate and increasing symptoms) with class 1 as reference. N=201				
Variable	**Bivariate models**		**Multivariate model**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.99 (0.94; 1.03)	0.523		
Gender	0.67 (0.31; 1.48)	0.323		
Education, years	1.04 (0.94; 1.16)	0.462		
MMSE sum	0.99 (0.91; 1.09)	0.904		
CDR change	1.14 (1.03; 1.25)	**0.009**	1.14 (1.03; 1.25)	**0.009**
ADL sum	0.98 (0.87; 1.11)	0.767		
Cardiovascular diseases	0.26 (0.50; 1.38)	0.114		
APOE 4 carrier	1.07 (0.24; 4.66)	0.932		
MTA	0.68 (0.42; 1.12)	0.132		
WMH	1.01 (0.65; 1.57)	0.972		
Antidepressant (yes/no)	2.73 (0.96; 7.75)	0.059		
aMCI vs. dementia	2.22 (0.86; 5.73)	0.101		