Amyloid Burden and Depressive Symptom Trajectories in Older Adults at Risk of Developing Cognitive Decline

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ABSTRACT

Objective: Little is known about the amyloid load impact on depressive symptoms or disorders, although it can modulate the cognitive trajectory in older adults. Here, we analyzed, in individuals at risk of Alzheimer's dementia, the relationship between amyloid load and depressive symptoms changes over time.

Methods: This study included ≥ 70-year-old participants from the French Multidomain Alzheimer Preventive Trial (MAPT) (May 2008 to February 2011) who underwent brain amyloid load measurement by β-amyloid-[18F] florbetapir-PET at baseline and had spontaneous memory complaints and/or limitation in 1 instrumental activity of daily living or slow walking gait (N = 264). Symptoms of depression were measured with the Geriatric Depression Scale–15 items (GDS) at baseline and 6, 12, 24, and 36 months of follow-up. Four GDS factors were determined by principal component analysis (PCA): life satisfaction, level of apathy, self-esteem, and anxiety. Amyloid positive status was defined based on the amyloid load in 6 Alzheimer's dementia–related regions. Regional amyloid load was based on 3 dimensions defined by PCA. The longitudinal links between depressive symptomatology and amyloid load (ie, cortical AV45 and amyloid load dimensions) were analyzed using linear mixed-multivariate models.

Results: At baseline, 11% of participants had depressive symptoms (GDS > 5) and 34% were amyloid-positive. The global amyloid load was not associated with worsening of the total GDS score but only with the impairment of self-esteem factor during the follow-up after adjustment for age, sex, education level, and drug intake, dementia, and Mini-Mental State Examination score (β = –0.029, 95% CI [–0.052 to –0.007], *P* = .003). Regional amyloid load in hippocampus and bilateral caudate nucleus protected significantly from self-esteem decrease during the 3-year follow-up.

Conclusions: Although amyloid load shows no impact on GDS score in subjects at risk of Alzheimer's dementia, amyloid load may influence the progression of depressive dimension (self-esteem) with different effects according to the regional burden.

Trial Registration: ClinicalTrials.gov identifier: NCT00672685

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Depressive disorders or symptoms and Alzheimer's dementia (AD) are often comorbid.[1] Depressive symptoms are associated with cognitive troubles,[2] excess disability,[3] and suicide risk in patients with AD.[4] Brain amyloid load reflects one of the pathophysiologic lesions of AD.[5,6] Importantly, biomarkers, such as amyloid brain load measured by positron emission tomography (PET) or cerebrospinal fluid amyloid β level, may help to identify subjects at risk of AD years before the beginning of clinical symptoms.

Therefore, it could be important to determine the influence of amyloid load not only directly on the cognitive decline trajectory, but also on other factors that can modulate such a trajectory, for instance depressive symptoms or depressive disorders. Previous studies using PET with the β-amyloid-[18F] florbetapir tracer (PET-AV45) have highlighted a relationship between amyloid load and depressive symptoms in older adults, even free of dementia. Specifically, amyloid deposits in several brain regions, mainly the frontal area, were associated with depression symptoms.[7] Amyloid load in the parietal, precuneus, and frontal cortices was positively associated with lifetime history of depressive symptoms in an elderly population without dementia.[8,9] Amyloid load has been also linked to older age at depression onset in a geriatric population,[10] to treatment resistance,[11] and to comorbid mild cognitive impairment.[12]

These findings have sometimes been confirmed using other amyloid tracers. Symptoms of depression were positively associated with lateral temporal and posterior cingulate 2-(1-{6-[(2-[F18] fluoroethyl)(methyl) amino]-2-naphthyl} ethylidene) malononitrile binding[13,14] along with trait anxiety in middle aged and older non-demented individuals.[13] Using the Pittsburgh Compound-B tracer, amyloid burden was shown to be significantly associated with depressive symptoms and major depressive episodes[15,16] and with increase of anxious-depressive symptoms in cognitively normal older adults.[17]

Clinical Points

- The relationship between brain amyloid deposits and depression symptoms has been well described in cross-sectional studies; however, little is known about the impact of amyloid load on depression symptom trajectories over time in elderly individuals at risk of Alzheimer's dementia.
- The amyloid load seems not to directly explain depression progression over time in a population of older adults at risk of Alzheimer's dementia.
- Clinicians should, however, consider precise evaluation of self-esteem during the follow-up of older patients at risk for cognitive decline and positive brain amyloid burden.

The relationship between amyloid load and depression has been well described in cross-sectional studies in dementia-free individuals[18]; however, little is known about the links between amyloid load and depressive symptom changes over time in individuals at risk of AD. Yet, it is important to better understand the factors that can play a role in the cognitive trajectory of subjects at risk of AD in order to modulate their potential prognostic impact. Here, we evaluated the longitudinal relationship between depressive symptoms assessed serially with the Geriatric Depression Scale–15 items (GDS) during 36 months and global and regional amyloid load measured by PET-AV45 in ≥ 70-year-old subjects at risk of AD.

METHODS

Participants

This study included 264 participants from the French Multidomain Alzheimer Preventive Trial (MAPT)-AV45 ancillary study[19,20] who underwent 1 PET-AV45 scan and had a clinical follow-up with a large battery of neuropsychological tests and the GDS 15 items. As described in the protocol published by Vellas et al,[19] the MAPT study is a multicentered (n = 13), randomized, placebo-controlled trial evaluating the efficacy of 3 therapeutic interventions: (1) supplementation with omega-3 fatty acid; (2) isolated multidomain intervention consisting of physical exercise, nutritional counseling, and cognitive stimulation; and (3) a combination of both interventions on the change of cognitive functions for a period of 3 years in subjects aged 70 years and older at risk for AD. The results of this clinical trial were negative for the primary outcome; thus, the arms of randomization were not added in our analyses.[20] Patients were enrolled and randomly allocated between May 30, 2008, and February 24, 2011.

A study led by Vinkers et al[21] showed that the GDS–15 items is adapted to detect longitudinal modifications of depressive symptoms. GDS was also used to assess the evolution of depressive phenotype with time in cognitively normal adults.[17]

Individuals (70 years of age or older) were included in the parent MAPT study if they had spontaneous memory complaints, limitation in 1 instrumental activity of daily living, or slow walking gait (< 0.8 m/s) but were free of dementia. Exclusion criteria were a Mini-Mental State Examination (MMSE) score lower than 24, dependency for the basic activities of daily living (Index of ADL score lower than 6 [range, 0–6]),[22] any disease that could compromise the subject's participation (such as stroke or deafness), and previous supplementation with omega-3. Sociodemographic characteristics, comorbid psychiatric disorders, treatments, and depressive symptoms were assessed at baseline. Patients were included after they received a full explanation of the study nature and signed a written informed consent form. All experimental methods were carried out in accordance with the ethical guidelines determined by the French National Ministry of Health, Labor, and Welfare and by the Declaration of Helsinki. This study was approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer II, Toulouse).

Demographic Data and Depressive Symptoms Evaluation

The following sociodemographic data were collected: age, sex, and education level (undergraduate/postgraduate). The 15-item GDS was used to measure the level of depressive symptoms[23] at inclusion and then at months 6, 12, 24, and 36 of the follow-up. Symptoms of depression were identified when the GDS score was > 5, similarly to other studies.[24,25] Cognitive performances were assessed with the MMSE[26] and the Clinical Dementia Rating scale (CDR)[27] at baseline. Comorbid psychiatric disorders were evaluated using the *DSM-IV* criteria, and apolipoprotein E allele 4 (APOE4) status was characterized. Psychotropic treatment intake was recorded at inclusion and coded according to the Anatomic Therapeutic Chemical Classification System.

Brain [18F] Florbetapir PET Imaging

PET-AV45 imaging was performed at 5 centers in France (Toulouse, Montpellier, Bordeaux, Limoges, and Nice). All scans began 50 minutes after injection on average of 4 MBq/kg of [18F] florbetapir. Images were acquired on 5 different hybrid PET–computed tomography scanners. PET sinograms were reconstructed with an iterative algorithm with corrections for randomness, scatter, photon attenuation, and decay. The algorithm produced images with an isotropic voxel of 2 × 2 × 2 mm^3 and a spatial resolution of approximately 5-mm full width at half maximum at the field of view center. PET-AV45 images were coregistered to an [18F] florbetapir template provided by Avid Radiopharmaceuticals (Philadelphia, PA) using SPM, to allow normalization to the Montreal Neurological Institute space. Cortical tracer retention was quantified using the standardized uptake value ratio (SUVr) relative to the whole cerebellum. Regional SUVr values were computed in 6 cortical regions of interest (frontal, parietal, temporal, precuneus, anterior and posterior cingulate cortices) that were averaged to create a global cortical SUVr. Amyloid load was assessed independently by 3 operators in function of the florbetapir cortical retention levels. The 3 operators, specialists in molecular imaging and blinded to all

clinical and diagnostic information, were trained by AVID Radiopharmaceuticals. Patients were classified as AV45-positive if the amyloid burden was pathologic according to the operators' collegial expertise.[19]

Statistical Analysis

The sample was described using percentages for categorical variables and medians, minimum (Min), and maximum (Max) for quantitative variables. To identify potential confounders, the associations between GDS score, amyloid load, and sociodemographic and clinical variables were tested using the Student *t* test or the Wilcoxon rank sum test when variables were non-normally distributed. Standardized principal component analysis (PCA) was carried out to determine the neuro-anatomic domains that represented the brain amyloid load distribution. Moreover, following the procedure used by Friedman et al[28], a PCA with promax rotation was carried out using standardized GDS items to determine the main principal dimensions of the depressive symptomatology. This analysis was carried out for each time step to prevent non-homogeneity of the constructs established and bias of the variance estimated due to repeated measurement. Results showed qualitatively similar factor structure and similar proportion of explained inertia during the 3 years of follow-up. Scores for 2 of the 4 dimensions were inverted to match the constructs of self-esteem and life satisfaction.

Then, the longitudinal links between depressive symptomatology (ie, total GDS score and GDS dimension separately) and amyloid load (ie, cortical AV45 and amyloid load dimensions) were analyzed using linear mixed-multivariate models with an individual random effect. A single linear multivariate mixed model was used to assess (1) the changes of depressive symptoms (total GDS score and each dimension) during the follow-up; (2) the effect of the amyloid load (AV45 status and regional dimensions) on depression (total GDS score and dimensions); and (3) whether the depressive symptom trajectory varied according to the AV45 status and regional amyloid load dimensions (interaction between time and amyloid load). *P* values were computed using the likelihood ratio test and Bonferroni correction with k = 9 (4 main effects and 5 interactions for each outcome). As there is no a priori about the existence of interactions between time and amyloid load on the depression level, each interaction was tested after removing from the model the other nonsignificant interactions. Continuous variables were log transformed and amyloid load dimensions were transformed in tertile classes to match the normality and linearity assumptions, respectively. The scale of time was the year, and results on figures were back transformed to allow interpretation in original scale. The unit of change for GDS factors is the standard deviation. Associations were adjusted according to 2 models: model 1 (M1), adjusted for the main sociodemographic variables (age, sex, and education level), treatments (antidepressants and anticonvulsants), and CDR status, and model 2 (M2), adjusted as for M1 and also for the MMSE score evaluated at each follow-up. Treatment arms were first included in the models and were systematically removed as no significant effects on GDS score or GDS dimensions (*P* value < .4) were found.

All statistical analyses were done with the R software (R Development Core Team 2005).

RESULTS

Sample Description

Among the 270 patients with PET-AV45 images, 6 patients were excluded because of missing data or absence of any follow-up visit. During the 3-year follow-up, 224 individuals went to all 4 follow-up visits (M6 to M36), 30 to 3, 7 to 2, and 3 to only 1. Therefore, the analysis included 264 participants. Two individuals were not evaluated for GDS at inclusion and dropped from the clinical description, leaving 262 participants (n = 158 women) with a median age of 74 years (ranging from 70 to 88) and MMSE score of 28 (ranging from 24 to 30). The baseline GDS score indicated that 29/262 patients (11%) had a GDS score > 5 and that 88/262 (34%) were AV45 positive. Comparison of the sociodemographic characteristics according to the GDS score (Table 1) did not highlight any difference between patients with depressive symptoms (n = 29) and non-symptomatic participants (GDS ≤ 5; n = 233) concerning age, sex, education level, intervention group (omega-3 supplementation + multidomain intervention, omega-3, multidomain intervention, or placebo), psychotropic drug intake (antidepressant and anticonvulsant), MMSE score, CDR status, APOE4 status, and AV45 positivity (34% and 31%) at baseline. There were no significant differences in SUVr, AV45 status, or baseline GDS score according to scanners and study centers.

Determination of Cerebral Dimensions and Depressive Factors by PCA

PCA allowed distinguishing of 3 amyloid regional dimensions: dimension 1 (frontal, parietal, temporal, precuneus, anterior and posterior cingulate cortices), dimension 2 (pontine region), and dimension 3 (hippocampus and bilateral caudate nuclei), all explaining 85.1% of the total variation (dimension 1: 65.8%, dimension 2: 11.1%, and dimension 3: 8.2%; see Supplementary Table 1 for the weight of each variable on the 3 components).

PCA of the GDS items showed the predominance of 4 factors after promax rotation: factor 1 (global level of life satisfaction), factor 2 (level of apathy), factor 3 (level of self-esteem), and factor 4 (level of anxiety) (see Supplementary Table 2). These 4 principal components explained 48.9% of the total variance.

Association Between Amyloid Load and Total GDS Score or GDS Factors (Independent of Time) at Baseline

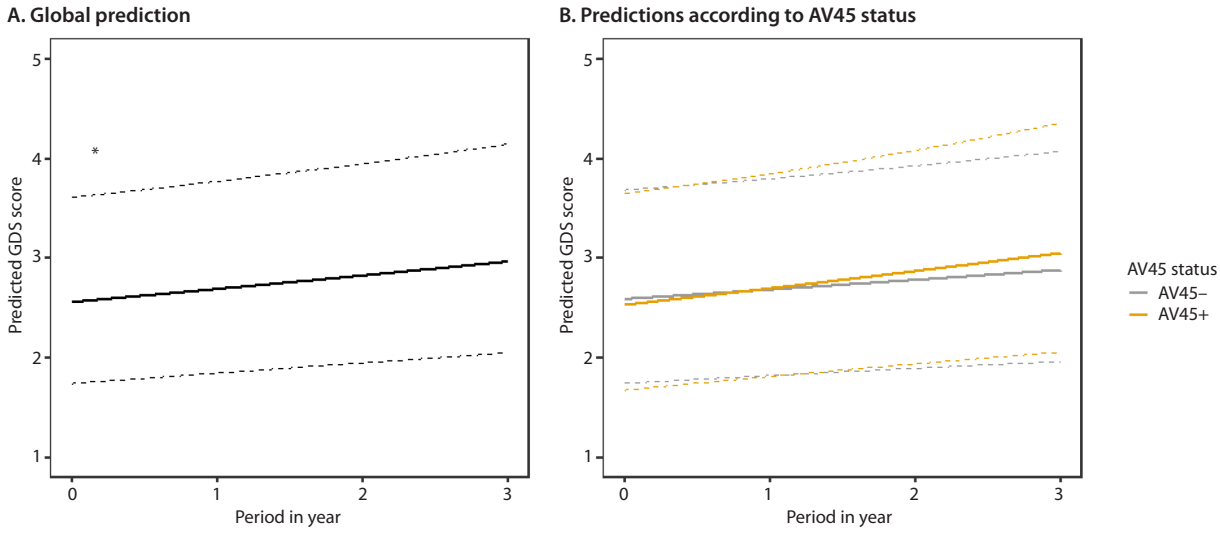
At baseline, linear mixed-multivariate models did not find any association between total GDS and AV45 status or regional amyloid load dimensions, even after inclusion of

Table 1. Clinical Characteristics According to the Total GDS Score Cutoff for Depression

Variables	GDS at inclusion ≤ 5 (n = 233)	GDS at inclusion > 5 (n = 29)	*P* Value
Sex (women), n (%)	139 (59.7)	19 (65.5)	.68
Age, median [min; max], y	74 [70; 88]	72 [70; 88]	.38
Education level (undergraduate), n (%)	126 (54.1)	18 (62.1)	.54
MAPT group, n (%)			
Omega-3 + multimodal intervention	62 (26.6)	9 (31)	.47
Omega-3	53 (22.7)	5 (17.2)	
Multimodal intervention	56 (24.0)	10 (34.5)	
Placebo	62 (26.6)	5 (17.2)	
AV45 amyloid status, n (%)			
Negative	154 (66.1)	20 (69)	.92
Positive	79 (33.9)	9 (31)	
SUVr, median [min; max]	1.12 [0.86; 1.71]	1.14 [0.95; 1.47]	.5
SUVr < 1.17, n (%)	146 (62.7)	15 (51.7)	.35
SUVr ≥ 1.17, n (%)	87 (37.3)	14 (48.3)	
MMSE score (at inclusion), median [min; max]	29 [24; 30]	28 [24; 30]	.47
CDR status, n (%)			
No	145 (62.2)	9 (31)	.002
Questionable	88 (37.8)	20 (69)	
APOE4 carrier status, n (%)			
No	144 (71.3)	20 (74.1)	.94
Yes	58 (28.7)	7 (25.9)	
Antidepressant intake, n (%)			
No	218 (93.6)	27 (93.1)	.99
Yes	15 (6.4)	2 (6.9)	
Anticonvulsant intake, n (%)			
No	227 (97.4)	29 (100)	.99
Yes	6 (2.6)	0 (0)	

Abbreviations: APOE4 = apolipoprotein E allele 4, AV45 = AV45 variable, CDR = Clinical Dementia Rating, GDS = Geriatric Depression Scale–15 item, MAPT = Multidomain Alzheimer Preventive Trial, MMSE = Mini-Mental State Examination, SUVr = standardized uptake value ratio.

Figure 1. Mean Predicted GDS Score Across the Follow-up (Solid Curve) With 95% Confidence Intervals (Dotted Curve)



*Significance of association: $P < .05$.
Abbreviation: GDS = Geriatric Depression Scale–15 item.

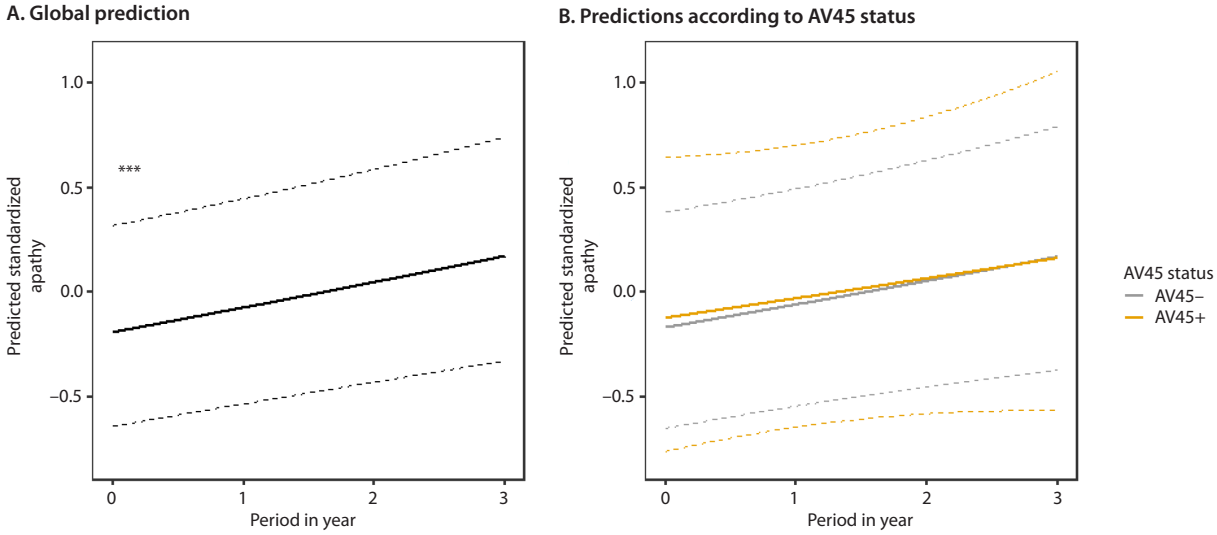
confounding factors in the models (Supplementary Tables 3 and 4).

Association Between Amyloid Load and Depressive Symptoms Changes During the 3-Year Follow-up

During the follow-up, the total GDS score increased significantly (M1 β = 0.032, 95% CI [0.003 to 0.062], $P = .02$; and M2 β = 0.032, 95% CI [0.002 to 0.062], $P = .03$; Figure 1), as did the apathy level (M1 β = 0.033, 95% CI [0.012 to 0.054], $P < .0001$ and M2 β = 0.032, 95% CI [0.012 to 0.053], $P < .0001$; Figure 2), in the whole population (Table 2).

Self-esteem decreased significantly during follow-up (M1 β = −0.012, 95% CI [−0.022 to −0.001], $P = .02$ and M2 β = −0.011, 95% CI [−0.022 to −0.001], $P = .03$).

Figure 2. Mean Predicted Apathy GDS Dimension Score Across the Follow-up (Solid Curve) With 95% Confidence Intervals (Dotted Curve)



***Significance of association: $P < .001$.
Abbreviation: GDS = Geriatric Depression Scale–15 item.

Table 2. Significant Associations Between Log(GDS), Log(GDS Factors), and Amyloid Deposition (AV45 Status and Regional Dimensions) According to the Two Adjusting Models

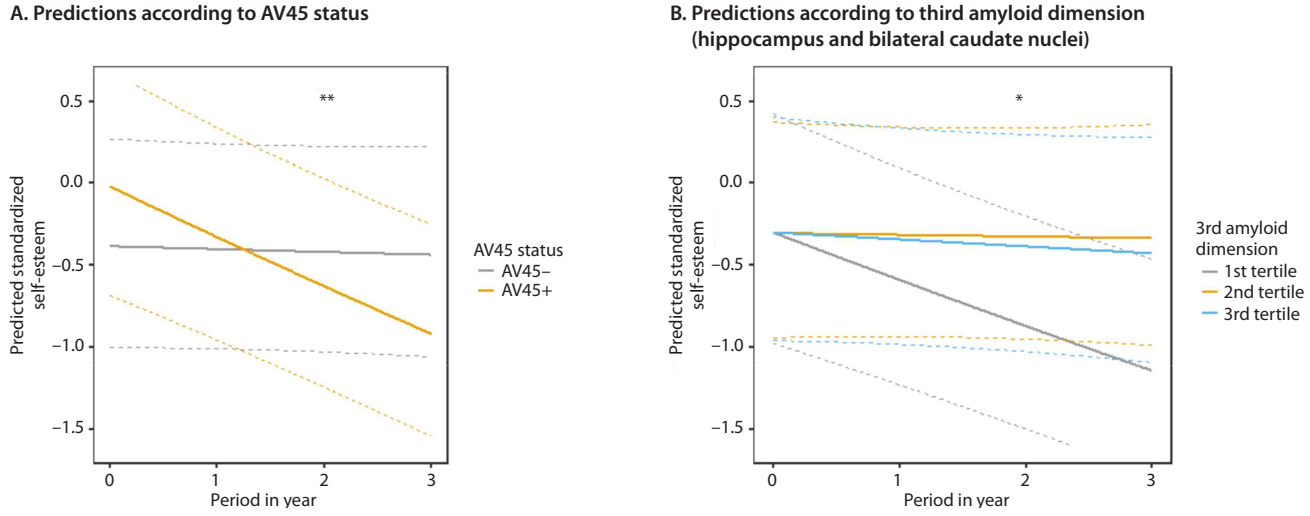
		Model 1[a]		Model 2[b]	
Outcomes	Variables	β [95% CI]	*P* value (LRT)	β [95% CI]	*P* value (LRT)
Log(global GDS)	Time (main effect)[c]	0.032 [0.003 to 0.062]	**.02**	0.032 [0.002 to 0.062]	**.03**
Log(self-esteem)	Time (main effect)	−0.012 [−0.022 to −0.001]	**.02**	−0.011 [−0.022 to −0.001]	**.03**
	AV45 (main effect)	−0.005 [−0.056 to 0.046]	.78	0.001 [−0.049 to 0.051]	.95
	Time × AV45	−0.032 [−0.054 to −0.009]	**.0007**	−0.029 [−0.052 to −0.007]	**.003**
	Time × med ter Dim 3	0.033 [0.007 to 0.059]	**.004**	0.031 [0.005 to 0.057]	**.01**
	Time × upp ter Dim 3	0.03 [0.004 to 0.056]		0.028 [0.002 to 0.054]	
Log(life satisfaction)	Time (main effect)	−0.01 [−0.021 to 0.002]	.16	−0.01 [−0.021 to 0.002]	.17
	Time × med ter Dim 3	0.026 [−0.002 to 0.054]	.06	0.026 [−0.003 to 0.054]	.08
	Time × upp ter Dim 3	0.03 [0.001 to 0.058]		0.029 [0.001 to 0.057]	
Log(apathy)	Time (main effect)	0.033 [0.012 to 0.054]	**<.0001**	0.032 [0.012 to 0.053]	**<.0001**
Log(anxiety)	Time (main effect)	0.005 [−0.012 to 0.022]	.44	0.005 [−0.012 to 0.022]	.41
	Time × med ter Dim 2	0.047 [0.004 to 0.09]	**.006**	0.047 [0.004 to 0.091]	**.005**
	Time × upp ter Dim 2	−0.008 [−0.051 to 0.035]		−0.008 [−0.051 to 0.035]	

[a]Model 1 adjusted for sex, age, education, drug intake (antidepressant and anticonvulsant), and CDR status.
[b]Model 2 adjusted for sex, age, education, drug intake (antidepressant and anticonvulsant), onset CDR status, and MMSE score.
[c]The main effects and interactions (×) with time are presented when statistically significant according to the LRT.
Abbreviations: AV45 = AV45 variable, CDR = Clinical Dementia Rating, Dim 2 = amyloid regional dimension 2 (pontine region), Dim 3 = amyloid regional dimension 3 (hippocampus and bilateral caudate nuclei), GDS = Geriatric Depression Scale–15 item, LRT = likelihood ratio test, med ter = medium tercile, MMSE = Mini-Mental State Examination, upp ter = upper tercile.

Linear mixed-multivariate models did not find any association between AV45 status and total GDS score changes during the 3-year follow-up (Supplementary Table 3) or between global SUVr and total GDS score changes (results not shown). AV45 positive status was associated with decrease of self-esteem (−1 standard deviation in 3 years) even after adjusting for age, sex, education level, drug intake (antidepressant and anticonvulsant), and CDR status (M1 β = −0.032, 95% CI [−0.054 to −0.009], $P = .0007$) and MMSE score (M2 β = −0.029, 95% CI [−0.052 to −0.007], $P = .003$; Figure 3). However, in participants with amyloid load specifically in hippocampus and in the two caudate nuclei (second and third tertiles of the dimension 3), self-esteem level decreased less over time (M1 β = 0.033, 95% CI [0.007 to 0.059], $P = .004$ and M2 β = 0.031, 95% CI [0.005 to 0.057], $P = .01$; Figure 3). In the same line, life satisfaction level decreased less over time in those individuals, but this association was not statistically significant (M1 β = 0.026, 95% CI [−0.002 to 0.054], $P = .06$ and M2 β = 0.026, 95% CI [−0.003 to 0.054], $P = .08$; Figure 4).

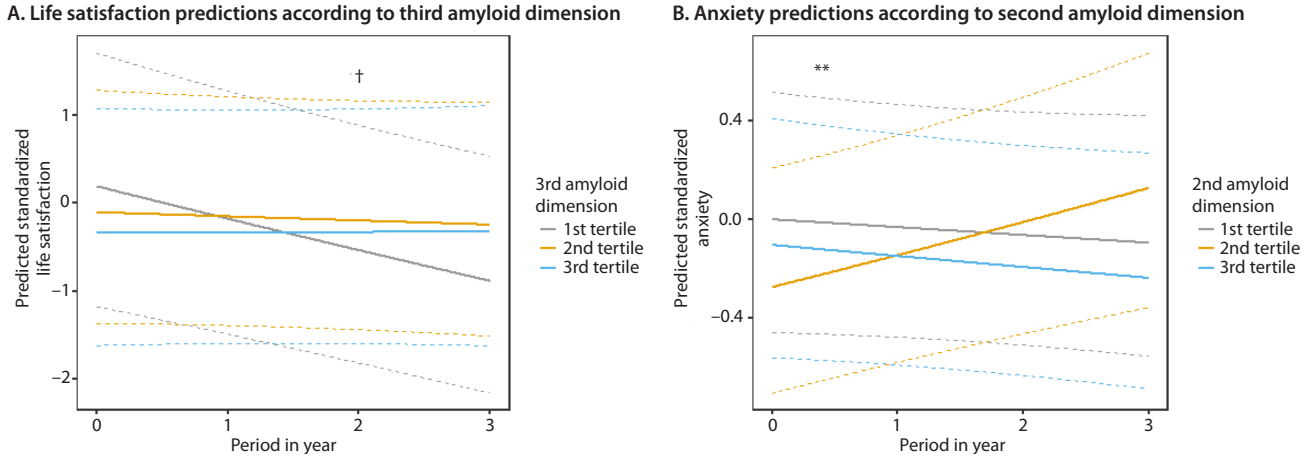
On the other hand, anxiety level increased more during the follow-up in participants with intermediate amyloid deposits in the pontine region (second tertile dimension 2) (M1 β = 0.047, 95% CI [0.004 to 0.09], $P = .006$ and M2 β = 0.047, 95% CI [0.004 to 0.091], $P = .005$; Figure 4). No association was found between brain amyloid deposits and apathy level changes (Figure 2). We performed a sensitivity analysis to evaluate the effect of treatment arms on these associations by

Figure 3. Mean Predicted Self-Esteem GDS Dimension Score Across the Follow-up (Solid Curve) With 95% Confidence Intervals (Dotted Curve)



*Significance of association: $P < .05$.
**Significance of association: $P < .01$.
Abbreviation: GDS = Geriatric Depression Scale–15 item.

Figure 4. Mean Predicted (A) Life Satisfaction and (B) Anxiety GDS Dimension Scores Across the Follow-up (Solid Curve) With 95% Confidence Intervals (Dotted Curve) According to the Third and the Second Amyloid Dimensions, Respectively



†Significance of association: $P < 0.1$.
**Significance of association: $P < .01$.
Abbreviation: GDS = Geriatric Depression Scale–15 item.

adding them to the best fitted models. The results remained qualitatively unchanged (Supplementary Table 5).

DISCUSSION

Our study shows that the amyloid load does not directly explain the progression of the total GDS score over time in a population of older adults at risk of AD. However, global brain amyloid load seems to be associated with decrease of self-esteem, independently of age, sex, sociocultural level, and cognitive status. Conversely, amyloid deposits in hippocampus and caudate nuclei seem to be linked with a lower impairment of self-esteem.

First, we found an association between diffuse brain amyloid deposits and self-esteem reduction over time. Interestingly, Pruessner et al[29] reported also an interaction between low level of self-esteem and age-related gray matter volume decline. Low self-esteem level is a key factor for determining the general health outcomes and quality of life in older adults,[30] as well as a specific risk factor for depression throughout life.[31] Low self-esteem and depressive symptoms show a bidirectional relationship, and low self-esteem is generally considered a risk factor of depression independently of age according to a meta-analysis.[32] A decrease in self-esteem level may worsen depression and favor its chronicity.[33] The link between low self-esteem and

depression may be mediated by higher cortisol secretion.[34] Therefore, individuals with reduced levels of self-esteem might be more prone to appraise challenging life events as threats and to develop dysregulated stress responses, leading to symptoms of depression. Moreover, self-esteem might play a role in the response to depression treatment.[35]

Moreover, we found that amyloid deposition in the hippocampus may be associated with lower self-esteem decrease, but not with life satisfaction, in a population of old people at risk of physical and cognitive decline. These results are not in line with the findings reported by Pruessner et al, who found an association between small hippocampal volume and self-esteem decline in a population of healthy 60- to 84-year-old adults.[29] A population-based cohort study showed that baseline cognitive abilities, self-regulative skills, and perceived control are strong predictors of self-esteem in old age.[36] Both findings support the hypothesis that cognitive level deterioration and damaged hippocampus constitute a risk factor for low self-esteem through a failure of source monitoring for negative life events and the generalization of negative self-perceptions. Our participant sample at risk for cognitive decline showed a decrease of self-esteem level during the 3-year follow-up. Although it has been reported that self-esteem is globally a stable personality trait in healthy old adults, with minor variations, it tends to decrease in very late life.[36,37] Hence, being at risk for cognitive decline may be a risk factor for self-esteem impairment over time. Further studies are needed to confirm these results and determine the potential causality between regional brain structure modifications and self-esteem decrease in older adults.

Surprisingly, amyloid deposition in the frontal lobe was not associated with apathy level worsening in our study. Recent cross-sectional studies have reported a link between these variables in patients with AD[38] and in a population of individuals with mild cognitive impairment.[39]

Our negative results could be explained by the nonspecific assessment of this clinical dimension in our sample because the GDS is not designed for apathy evaluation, differently from the Neuropsychiatric Inventory,[40] for instance.

Our study has some limitations. The 4 evaluated dimensions (self-esteem, life satisfaction, apathy, and anxiety) were not assessed with specific clinical scales but were extracted from the GDS items using the method described by Friedman et al.[28] However, the GDS factor structure identified in our study is similar to the one previously described in a population of ≥ 60-year-old patients hospitalized in geriatric and internal medicine wards.[41] Our sample included only 30 participants with depressive symptoms (GDS > 5) (ie, 11% of the total population). Although this rate is coherent with literature findings in Europe in a population of non-demented older adults,[42,43] the low proportion of patients with a clinically significant level of depressive symptoms limits us in drawing conclusions and generalizing the results about the link between brain amyloid deposits and depressive symptomatology. In fact, depressive symptoms could make some patients at risk for AD more likely to miss the evaluation.[44] The low prevalence of depressive symptoms may explain the lack of association between amyloid burden and some depressive dimensions such as life satisfaction. The MAPT study is an interventional clinical trial with different multimodal interventions, including omega-3 supplementation. As the primary objective of the clinical trial was negative, we did not adjust our analysis in function of the randomization arm.[20] Finally, as the amyloid regional dimension 3 (involving hippocampus and bilateral caudate nuclei) explains a moderate part of the variation of the total amyloid load (8.2%), quantitative interpretations of its effect on the depressive symptomatology should be made with caution.

The present study has also several strengths. This is the first study providing a longitudinal evaluation of a large sample of outpatients at AD risk. We analyzed the total GDS score and also different dimensions of depression. In addition, recent studies reported that PET-AV45 efficiently detects amyloid deposition in brain.[9,10] Finally, we assessed the impact of regional amyloid load.

To conclude, the diffuse brain amyloid load (AV45 status) has no impact on the worsening of total GDS score over time in subjects at risk of AD. This suggests that other factors might interfere with the global level of depressive symptoms in this population and need to be identified in order to propose specific personalized strategies to slow down cognitive decline. Interestingly, amyloid load might have an impact on the progression of specific depressive dimensions (such as self-esteem) with different effects according to regional patterns in subjects at risk of AD. Our results should be confirmed using specific clinical tools to evaluate these dimensions. The analysis of regional PET amyloid profiles may help to anticipate potential trajectories of depressive dimensions in non-demented individuals, and then to propose adapted preventive strategies.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Amyloid Burden and Depressive Symptoms Trajectories in Older Adults at Risk of Developing Cognitive Decline

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List of Supplementary Material for the article

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	Dimension 1	Dimension 2	Dimension 3
HIPPO	0.633		0.586
PONS		0.879	
CSO	0.582	0.551	
P_CING	0.830		
PREC	0.890		
FR_MOR	0.829		
FR_MOC	0.924		
FR_PAR	0.863		
TEMP	0.920		
A_CING	0.927		
PUTP_L	0.772	0.530	
PUTP_R	0.841		
PUTA_L	0.923		
PUTA_R	0.891		
CAU_L	0.719		0.619
CAU_R	0.736		0.598
G_MAT	0.965		

Supplementary table 1. Correlations between cerebral amyloid load in different brain regions and the three first components of the principal component analysis, representing 65.8%, 11.1%, and 8.2%, respectively, of the total inertia (Eigen value >1 for all).
CAU: caudate nucleus; CSO: centrum semi-ovale; FR_PAR: fronto-parietal cortex; Hippo: Hippocampus; P_Cing: posterior cingulate; Prec: precuneus; PUTP: posterior putamen; Temp: temporal cortex.

GDS items	life satisfaction	Apathy	self-esteem	level of anxiety
Are you basically satisfied with your life?	0.75			
Have you dropped many of your activities and interests?		0.64		
Do you feel that your life is empty?	0.67			
Do you often get bored?	0.61			
Are you in good spirits most of the time?	0.55			
Are you afraid that something bad is going to happen to you?				0.97
Do you feel happy most of the time?	0.82			
Do you often feel helpless?				0.49
Do you prefer to stay at home, rather than going out and doing new things?		0.89		
Do you feel you have more problems with memory than most people?			0.53	
Do you think it is wonderful to be alive?				
Do you feel pretty worthless the way you are now?	0.3		0.39	
Do you feel full of energy?		0.51		
Do you feel that your situation is hopeless?	0.33		0.44	
Do you think that most people are better off than you are?			0.66	

Supplementary table 2. Correlations between the 15 Geriatric Depression Scale items and the identified factors after principal component analysis with promax rotation. The four components represent 18.6%, 11.4%, 9.4%, and 9.6%, respectively, (48.9%) of total inertia after rotation (Eigen value >1 for all before rotation).

		Model 1		Model 2	
Outcomes	**Variables**	**M1 betas [95%IC]**	**M1 p-value (LRT)**	**M2 betas [95%IC]**	**M2 p-value (LRT)**
log(Global GDS)	intercept	1.138[0.958;1.319]		1.484[0.681;2.287]	
	age z-scored	0.103[0.002;0.204]	**0.04**	0.101[0;0.202]	**0.047**
	gender	-0.065[-0.262;0.133]	0.36	-0.066[-0.263;0.131]	0.35
	education	-0.131[-0.325;0.063]	0.52	-0.126[-0.32;0.068]	0.62
	score MMSE			-0.012[-0.04;0.015]	0.22
	CDR status	0.103[-0.095;0.3]	0.14	0.096[-0.101;0.294]	0.17
	antiepileptic intake	-0.036[-0.687;0.616]	0.88	-0.031[-0.681;0.619]	0.89
	antidepressant intake	0.416[0.02;0.812]	0.03	0.412[0.017;0.807]	0.03
	AV45 status	0.008[-0.197;0.214]	0.91	0.002[-0.204;0.207]	0.98
	time	0.032[0.003;0.062]	**0.02**	0.032[0.002;0.062]	**0.03**
	Interaction Time x AV45	0.02[-0.044;0.083]	0.39	0.017[-0.047;0.081]	0.46
log(Life satisfaction)	intercept	2.587[2.52;2.653]		2.489[2.181;2.797]	
	age z-scored	-0.009[-0.046;0.028]	0.5	-0.008[-0.045;0.029]	0.54
	gender	0.008[-0.065;0.08]	0.76	0.008[-0.064;0.081]	0.75
	education	0.047[-0.024;0.118]	0.58	0.045[-0.026;0.117]	0.67
	score MMSE			0.003[-0.007;0.014]	0.37
	CDR status	-0.023[-0.096;0.049]	0.37	-0.021[-0.094;0.051]	0.41
	antiepileptic intake	0.044[-0.195;0.283]	0.61	0.042[-0.197;0.282]	0.62
	antidepressant intake	-0.095[-0.241;0.05]	0.59	-0.094[-0.239;0.051]	0.62
	AV45 status	0.011[-0.064;0.087]	0.68	0.013[-0.063;0.088]	0.63
	time	-0.01[-0.021;0.002]	0.16	-0.01[-0.021;0.002]	0.17
	Interaction Time x AV45	0.001[-0.024;0.025]	0.92	0.002[-0.023;0.026]	0.85
log(Apathy)	intercept	1.211[1.118;1.305]		1.5[0.971;2.029]	
	age z-scored	0.071[0.02;0.122]	**0.001**	0.069[0.018;0.121]	**0.002**

		Model 1		Model 2	
	gender	0.018[-0.083;0.118]	0.62	0.017[-0.084;0.117]	0.64
	education	-0.049[-0.148;0.049]	0.16	-0.045[-0.144;0.054]	0.2
	score MMSE			-0.01[-0.028;0.008]	0.13
	CDR status	-0.001[-0.101;0.099]	0.98	-0.006[-0.107;0.095]	0.86
	antiepileptic intake	-0.068[-0.399;0.263]	0.56	-0.064[-0.396;0.268]	0.59
	antidepressant intake	0.25[0.049;0.451]	**0.005**	0.246[0.045;0.447]	**0.006**
	AV45 status	0.007[-0.098;0.111]	0.86	0.001[-0.103;0.106]	0.97
	time	0.033[0.012;0.054]	**<0.0001**	0.032[0.012;0.053]	**<0.0001**
	Interaction Time x AV45	-0.005[-0.049;0.04]	0.77	-0.007[-0.052;0.037]	0.66
log(Self-esteem)	intercept	2.33[2.285;2.376]		1.998[1.734;2.261]	
	age z-scored	-0.012[-0.037;0.013]	0.17	-0.01[-0.034;0.015]	0.27
	gender	-0.032[-0.08;0.017]	0.6	-0.031[-0.078;0.017]	0.66
	education	0.039[-0.009;0.087]	0.21	0.034[-0.013;0.081]	0.41
	score MMSE			0.012[0.003;0.021]	**0.003**
	CDR status	-0.044[-0.093;0.005]	0.11	-0.038[-0.086;0.011]	0.26
	antiepileptic intake	0.07[-0.091;0.231]	0.22	0.066[-0.093;0.224]	0.24
	antidepressant intake	-0.121[-0.219;-0.024]	**0.005**	-0.117[-0.213;-0.021]	**0.006**
	AV45 status	-0.005[-0.056;0.046]	0.78	0.001[-0.049;0.051]	0.95
	time	-0.012[-0.022;-0.001]	**0.02**	-0.011[-0.022;-0.001]	**0.03**
	Interaction Time x AV45	-0.032[-0.054;-0.009]	**0.0007**	-0.029[-0.052;-0.007]	**0.003**
log(Anxiety)	intercept	1.305[1.227;1.383]		1.112[0.674;1.549]	
	age z-scored	0.017[-0.026;0.059]	0.28	0.018[-0.025;0.061]	0.24
	gender	-0.051[-0.134;0.033]	0.8	-0.05[-0.134;0.034]	0.85
	education	-0.004[-0.086;0.078]	0.89	-0.007[-0.09;0.076]	0.81
	score MMSE			0.007[-0.008;0.022]	0.22
	CDR status	0.08[-0.004;0.164]	*0.07*	0.084[0;0.168]	**0.049**
	antiepileptic intake	0.085[-0.191;0.361]	0.39	0.082[-0.195;0.359]	0.4
	antidepressant intake	0.027[-0.141;0.194]	0.65	0.029[-0.139;0.197]	0.63

	Model 1		Model 2	
AV45 status	0.014[-0.073;0.101]	0.66	0.017[-0.07;0.105]	0.58
time	0.005[-0.012;0.022]	0.44	0.005[-0.012;0.022]	0.41
Interaction Time x AV45	0.026[-0.011;0.062]	0.47	0.027[-0.009;0.064]	0.34

Supplementary table 3: Multivariate analysis of the relationships between log(GDS), log(GDS factors) and amyloid deposition (AV45 status) according to the two models: M1, adjusted for sex, age, educational level, medication and CDR status; M2, adjusted for sex, age, educational level, medication, onset CDR status and MMSE score.

The two adjusting models are:
M1, adjusted for Sex, Age, education, medication and CDR status;
M2, adjusted for Sex, Age, education, medication, onset CDR status and MMSE score;
The p-value presented are the p-values from likelihood ratio tests (LRTs).
Abbreviations: AV45: AV45 variable; GDS: Geriatric Depression scale -15 item.

		Model 1		Model 2	
Outcomes	**Variables**	**M1 betas [95%IC]**	**M1 p-value (LRT)**	**M2 betas [95%IC]**	**M2 p-value (LRT)**
Global GDS	intercept	1.174[0.851;1.496]		1.411[0.569;2.254]	
	age z-scored	0.094[-0.008;0.196]	*0.09*	0.092[-0.01;0.194]	0.1
	gender	-0.083[-0.29;0.124]	0.25	-0.084[-0.291;0.123]	0.25
	education	-0.112[-0.308;0.084]	0.1	-0.109[-0.305;0.087]	0.12
	CDR status	0.095[-0.102;0.292]	0.17	0.091[-0.107;0.288]	0.19
	antiepileptic	0.022[-0.634;0.678]	0.92	0.025[-0.631;0.68]	0.92
	antidepressant	0.406[0.003;0.809]	**0.04**	0.404[0.001;0.806]	**0.042**
	score MMSE			-0.008[-0.036;0.019]	0.39
	Time	0.033[0.003;0.062]	**0.02**	0.032[0.002;0.062]	**0.02**
	Medium tertile Dim 1	0.077[-0.17;0.323]	0.68	0.076[-0.171;0.322]	0.68
	Upper tertile Dim 1	0.04[-0.21;0.289]		0.036[-0.213;0.285]	
	Medium tertile Dim 2	-0.023[-0.261;0.215]	0.86	-0.021[-0.258;0.217]	0.88
	Upper tertile Dim 2	-0.046[-0.286;0.194]		-0.043[-0.283;0.196]	
	Medium tertile Dim 3	-0.232[-0.474;0.009]	0.23	-0.227[-0.469;0.014]	0.26
	Upper tertile Dim 3	-0.142[-0.386;0.102]		-0.139[-0.383;0.106]	
	Inter Time x Med ter Dim 1	-0.002[-0.077;0.073]	0.68	-0.058[-0.32;0.203]	0.39
	Inter Time x upp ter Dim 1	-0.021[-0.097;0.054]		-0.003[-0.078;0.072]	
	Inter Time x Med ter Dim 2	0.014[-0.059;0.087]	0.48	0.014[-0.059;0.087]	0.49
	Inter Time x upp ter Dim 2	-0.046[-0.119;0.026]		-0.046[-0.118;0.027]	
	Inter Time x Med ter Dim 3	-0.057[-0.13;0.016]	0.18	-0.055[-0.129;0.018]	0.23
	Inter Time x upp ter Dim 3	-0.07[-0.143;0.003]		-0.068[-0.141;0.005]	
life satisfaction (log)	intercept	2.639[2.519;2.759]		2.574[2.251;2.896]	
	age z-scored	-0.008[-0.046;0.03]	0.53	-0.008[-0.046;0.03]	0.56
	gender	0.006[-0.071;0.083]	0.82	0.006[-0.07;0.083]	0.82
	education	0.047[-0.026;0.119]	0.62	0.046[-0.027;0.118]	0.67
	CDR status	-0.021[-0.094;0.052]	0.42	-0.02[-0.093;0.053]	0.44

		Model 1		Model 2	
	antiepileptic	0.045[-0.198;0.287]	0.6	0.044[-0.199;0.287]	0.61
	antidepressant	-0.089[-0.238;0.06]	0.82	-0.088[-0.238;0.061]	0.84
	score MMSE			0.002[-0.008;0.013]	0.54
	Time	-0.01[-0.021;0.002]	0.16	-0.01[-0.021;0.002]	0.17
	Medium tertile Dim 1	0.001[-0.09;0.092]	0.96	0.001[-0.09;0.093]	0.97
	Upper tertile Dim 1	-0.007[-0.099;0.085]		-0.006[-0.098;0.086]	
	Medium tertile Dim 2	-0.028[-0.116;0.06]	0.15	-0.029[-0.117;0.059]	0.15
	Upper tertile Dim 2	0.031[-0.058;0.12]		0.03[-0.058;0.119]	
	Medium tertile Dim 3	0.008[-0.082;0.097]	0.93	0.006[-0.083;0.096]	0.94
	Upper tertile Dim 3	-0.004[-0.094;0.087]		-0.005[-0.095;0.086]	
	Inter Time x Med ter Dim 1	0.004[-0.025;0.033]	0.57	0.005[-0.024;0.034]	0.54
	Inter Time x upp ter Dim 1	0.011[-0.018;0.04]		0.012[-0.018;0.041]	
	Inter Time x Med ter Dim 2	0.016[-0.013;0.044]	0.49	0.016[-0.013;0.044]	0.51
	Inter Time x upp ter Dim 2	0.024[-0.004;0.052]		0.024[-0.004;0.052]	
	Inter Time x Med ter Dim 3	0.026[-0.002;0.054]	*0.06*	0.026[-0.003;0.054]	*0.08*
	Inter Time x upp ter Dim 3	0.03[0.001;0.058]		0.029[0.001;0.057]	
Apathy (log)	intercept	1.21[1.038;1.382]		1.464[0.917;2.011]	
	age z-scored	0.066[0.014;0.118]	**0.003**	0.064[0.012;0.117]	**0.005**
	gender	-0.003[-0.109;0.102]	0.93	-0.004[-0.11;0.102]	0.91
	education	-0.036[-0.136;0.064]	0.31	-0.032[-0.133;0.068]	0.36
	CDR status	-0.003[-0.103;0.098]	0.94	-0.007[-0.109;0.094]	0.84
	antiepileptic	-0.04[-0.375;0.295]	0.73	-0.037[-0.373;0.298]	0.75
	antidepressant	0.24[0.035;0.446]	**0.009**	0.238[0.032;0.444]	**0.01**
	score MMSE			-0.009[-0.027;0.009]	0.18
	Time	0.033[0.012;0.054]	**<0.0001**	0.033[0.012;0.053]	**<0.0001**
	Medium tertile Dim 1	-0.01[-0.131;0.11]	0.92	-0.011[-0.132;0.11]	0.94
	Upper tertile Dim 1	0.007[-0.115;0.129]		0.003[-0.12;0.125]	
	Medium tertile Dim 2	0.007[-0.114;0.128]	0.92	0.01[-0.112;0.131]	0.92
	Upper tertile Dim 2	-0.01[-0.132;0.113]		-0.007[-0.129;0.116]	

		Model 1		Model 2	
	Medium tertile Dim 3	-0.079[-0.201;0.044]	0.52	-0.075[-0.198;0.049]	0.65
	Upper tertile Dim 3	-0.101[-0.225;0.023]		-0.098[-0.222;0.026]	
	Inter Time x Med ter Dim 1	-0.028[-0.08;0.025]	0.19	-0.029[-0.082;0.024]	0.16
	Inter Time x upp ter Dim 1	-0.032[-0.085;0.021]		-0.034[-0.087;0.019]	
	Inter Time x Med ter Dim 2	-0.015[-0.068;0.037]	0.62	-0.016[-0.068;0.037]	0.62
	Inter Time x upp ter Dim 2	-0.017[-0.069;0.036]		-0.017[-0.069;0.036]	
	Inter Time x Med ter Dim 3	-0.024[-0.075;0.028]	0.21	-0.022[-0.074;0.03]	0.26
	Inter Time x upp ter Dim 3	-0.032[-0.084;0.02]		-0.03[-0.082;0.022]	
Self-esteem (log)	intercept	2.348[2.264;2.432]		2.076[1.805;2.347]	
	age z-scored	-0.012[-0.037;0.014]	0.19	-0.01[-0.035;0.015]	0.28
	gender	-0.029[-0.08;0.022]	0.11	-0.028[-0.079;0.023]	0.12
	education	0.034[-0.014;0.083]	0.41	0.031[-0.018;0.079]	0.65
	CDR status	-0.041[-0.09;0.008]	0.16	-0.036[-0.085;0.012]	0.32
	antiepileptic	0.064[-0.099;0.226]	0.26	0.061[-0.1;0.222]	0.28
	antidepressant	-0.115[-0.214;-0.015]	**0.01**	-0.112[-0.211;-0.014]	**0.01**
	score MMSE			0.01[0;0.019]	**0.03**
	Time	-0.012[-0.022;-0.001]	**0.02**	-0.011[-0.022;-0.001]	**0.03**
	Medium tertile Dim 1	-0.029[-0.09;0.032]	0.35	-0.028[-0.088;0.033]	0.4
	Upper tertile Dim 1	-0.025[-0.086;0.037]		-0.02[-0.081;0.041]	
	Medium tertile Dim 2	0.004[-0.055;0.063]	0.53	0.001[-0.057;0.059]	0.58
	Upper tertile Dim 2	0.022[-0.037;0.081]		0.019[-0.04;0.078]	
	Medium tertile Dim 3	0.041[-0.019;0.101]	0.12	0.036[-0.023;0.095]	0.18
	Upper tertile Dim 3	0.036[-0.025;0.096]		0.032[-0.028;0.092]	
	Inter Time x Med ter Dim 1	0[-0.026;0.026]	0.46	0.001[-0.025;0.028]	0.56
	Inter Time x upp ter Dim 1	-0.01[-0.037;0.016]		-0.008[-0.035;0.018]	
	Inter Time x Med ter Dim 2	0.009[-0.016;0.035]	*0.09*	0.009[-0.016;0.035]	0.1
	Inter Time x upp ter Dim 2	0.028[0.002;0.053]		0.027[0.001;0.053]	
	Inter Time x Med ter Dim 3	0.033[0.007;0.059]	**0.004**	0.031[0.005;0.057]	**0.01**
	Inter Time x upp ter Dim 3	0.03[0.004;0.056]		0.028[0.002;0.054]	

		Model 1		Model 2	
level of anxiety (log)	intercept	1.385[1.241;1.528]		1.133[0.682;1.583]	
	age z-scored	0.014[-0.029;0.058]	0.36	0.016[-0.028;0.06]	0.3
	gender	-0.052[-0.141;0.036]	0.84	-0.051[-0.14;0.037]	0.9
	education	0.002[-0.082;0.085]	0.95	-0.002[-0.086;0.082]	0.95
	CDR status	0.076[-0.009;0.16]	0.1	0.08[-0.004;0.165]	*0.07*
	antiepileptic	0.103[-0.176;0.383]	0.29	0.101[-0.18;0.381]	0.31
	antidepressant	0.019[-0.153;0.191]	0.75	0.021[-0.151;0.193]	0.73
	score MMSE			0.009[-0.006;0.024]	0.1
	Time	0.005[-0.012;0.022]	0.44	0.005[-0.012;0.022]	0.41
	Medium tertile Dim 1	0.035[-0.08;0.13]	0.63	0.026[-0.08;0.131]	0.58
	Upper tertile Dim 1	0.035[-0.071;0.141]		0.038[-0.068;0.145]	
	Medium tertile Dim 2	-0.009[-0.114;0.096]	0.71	-0.01[-0.116;0.095]	0.69
	Upper tertile Dim 2	-0.03[-0.136;0.076]		-0.032[-0.138;0.075]	
	Medium tertile Dim 3	-0.079[-0.182;0.025]	0.88	-0.082[-0.186;0.022]	0.73
	Upper tertile Dim 3	-0.041[-0.146;0.063]		-0.044[-0.149;0.061]	
	Inter Time x Med ter Dim 1	0.037[-0.006;0.08]	0.45	0.038[-0.005;0.081]	0.38
	Inter Time x upp ter Dim 1	0.026[-0.017;0.069]		0.028[-0.016;0.071]	
	Inter Time x Med ter Dim 2	0.047[0.004;0.09]	**0.006**	0.047[0.004;0.091]	**0.005**
	Inter Time x upp ter Dim 2	-0.008[-0.051;0.035]		-0.008[-0.051;0.035]	
	Inter Time x Med ter Dim 3	-0.001[-0.043;0.042]	0.65	-0.002[-0.052;0.034]	0.59
	Inter Time x upp ter Dim 3	-0.012[-0.055;0.03]		-0.015[-0.045;0.04]	

Supplementary table 4: Multivariate analysis of the relationships between log(GD, log(GDS factors) and amyloid deposition (regional dimensions) according to the two models: M1, adjusted for sex, age, educational level, medication and CDR status; M2, adjusted for sex, age, educational level, medication, onset CDR status and MMSE score.

The two adjusting models are:
M1, adjusted for Sex, Age, education, medication and CDR status;

M2, adjusted for Sex, Age, education, medication, onset CDR status and MMSE score;
The p-value presented are the p-values from likelihood ratio test (LRT).
Abbreviations: GDS: Geriatric Depression scale -15 item; Dim 2: amyloid regional dimension 2 (pontine region): Dim 3: amyloid regional dimension 3 (hippocampus and bilateral caudate nuclei); med ter: medium tercile; upp ter: upper tercile;

Supplementary table 5:

Multivariate analysis of the relationships between GDS, GDS factors and amyloid deposition (AV45 status) according to the model adjusted for sex, age, education, medication, CDR status, MMSE score and treatment arms.

Outcomes	Variables	M3 betas [95%IC]	M3 p-value (LRT)
GDS	intercept	1.479[0.657;2.301]	
	age z-scored	0.101[-0.001;0.202]	0.047
	gender	-0.066[-0.265;0.132]	0.34
	education	-0.128[-0.324;0.068]	0.59
	score MMSE	-0.012[-0.039;0.016]	0.23
	arms omega3	-0.001[-0.283;0.28]	0.94
	arms IM	-0.041[-0.313;0.232]	
	arms ctrl	0.02[-0.25;0.291]	
	CDR status	0.103[-0.1;0.305]	0.15
	antiepileptic intake	-0.034[-0.691;0.622]	0.88
	antidepressant intake	0.411[0.01;0.813]	0.04
	AV45 status	-0.002[-0.212;0.207]	0.97
	time	0.032[0.002;0.062]	0.03
	Interaction Time x AV45	0.017[-0.046;0.081]	0.45
Life satisfaction	intercept	2.496[2.181;2.812]	
	age z-scored	-0.008[-0.045;0.029]	0.54
	gender	0.008[-0.065;0.081]	0.77
	education	0.046[-0.026;0.118]	0.65
	score MMSE	0.003[-0.007;0.014]	0.37
	arms omega3	-0.002[-0.106;0.102]	0.94
	arms IM	-0.02[-0.12;0.08]	
	arms ctrl	-0.011[-0.111;0.088]	
	CDR status	-0.019[-0.093;0.055]	0.47
	antiepileptic intake	0.04[-0.202;0.281]	0.64
	antidepressant intake	-0.096[-0.244;0.051]	0.59
	AV45 status	0.013[-0.064;0.091]	0.62
	time	-0.01[-0.021;0.002]	0.17
	Interaction Time x AV45	0.002[-0.023;0.026]	0.85
Apathy	intercept	1.494[0.955;2.034]	
	age z-scored	0.069[0.017;0.121]	0.002
	gender	0.016[-0.085;0.117]	0.65
	education	-0.045[-0.145;0.054]	0.2
	score MMSE	-0.01[-0.028;0.009]	0.14
	arms omega3	0.009[-0.134;0.153]	0.89
	arms IM	-0.026[-0.165;0.112]	
	arms ctrl	0.007[-0.131;0.145]	
	CDR status	-0.003[-0.106;0.1]	0.94
	antiepileptic intake	-0.069[-0.404;0.265]	0.56
	antidepressant intake	0.243[0.039;0.447]	0.008
	AV45 status	-0.001[-0.107;0.106]	0.99
	time	0.032[0.012;0.053]	0.0001
	Interaction Time x AV45	-0.007[-0.052;0.038]	0.66
Self-esteem	intercept	2.004[1.735;2.273]	
	age z-scored	-0.01[-0.034;0.015]	0.27
	gender	-0.031[-0.079;0.017]	0.64
	education	0.035[-0.013;0.082]	0.37
	score MMSE	0.012[0.002;0.021]	0.004
	arms omega3	0.003[-0.066;0.072]	0.94
	arms IM	-0.006[-0.072;0.06]	
	arms ctrl	-0.01[-0.076;0.055]	

Outcomes	Variables	M3 betas [95%IC]	M3 p-value (LRT)
	CDR status	-0.037[-0.086;0.012]	0.3
	antiepileptic intake	0.064[-0.096;0.223]	0.26
	antidepressant intake	-0.119[-0.217;-0.022]	0.005
	AV45 status	0.002[-0.049;0.053]	0.92
	time	-0.011[-0.022;-0.001]	0.03
	Interaction Time x AV45	-0.029[-0.052;-0.007]	0.002
Level of anxiety	intercept	1.115[0.669;1.561]	
	age z-scored	0.018[-0.025;0.061]	0.24
	gender	-0.05[-0.134;0.034]	0.83
	education	-0.006[-0.09;0.077]	0.83
	score MMSE	0.007[-0.008;0.022]	0.22
	arms omega3	0.003[-0.117;0.123]	0.99
	arms IM	-0.008[-0.124;0.107]	
	arms ctrl	-0.009[-0.124;0.106]	
	CDR status	0.085[-0.002;0.171]	0.05
	antiepileptic intake	0.08[-0.2;0.359]	0.42
	antidepressant intake	0.027[-0.144;0.197]	0.66
	AV45 status	0.018[-0.071;0.107]	0.57
	time	0.005[-0.012;0.022]	0.41
	Interaction Time x AV45	0.027[-0.009;0.064]	0.34

Abbreviations: AV45: AV45 variable; GDS: Geriatric Depression scale -15 item.

Supplementary table 6: Multivariate analysis of the relationships between GDS, GDS factors and amyloid deposition (regional dimensions) according to the model adjusted for sex, age, education, medication, CDR status, MMSE score and treatment arms.

Outcomes	Variables	M3 betas [95%IC]	M3 p-value (LRT)
GDS	intercept	1.431[0.569;2.293]	
	age z-scored	0.092[-0.011;0.195]	0.1
	gender	-0.085[-0.293;0.124]	0.24
	education	-0.11[-0.308;0.088]	0.11
	arms omega3	-0.042[-0.329;0.244]	0.89
	arms IM	-0.062[-0.338;0.215]	
	arms ctrl	0[-0.275;0.275]	
	CDR status	0.1[-0.102;0.302]	0.16
	antiepileptic	0.027[-0.635;0.689]	0.91
	antidepressant	0.412[0.004;0.82]	0.04
	score MMSE	-0.008[-0.036;0.02]	0.4
	Time	0.032[0.002;0.062]	0.02
	Medium tertile Dim 1	0.077[-0.173;0.326]	0.68
	Upper tertile Dim 1	0.031[-0.225;0.287]	
	Medium tertile Dim 2	-0.019[-0.259;0.221]	0.33
	Upper tertile Dim 2	-0.046[-0.291;0.198]	
	Medium tertile Dim 3	-0.231[-0.476;0.013]	0.24
	Upper tertile Dim 3	-0.138[-0.386;0.111]	
	Inter Time x Med ter Dim 1	-0.003[-0.078;0.072]	0.65
	Inter Time x upp ter Dim 1	-0.023[-0.099;0.053]	
	Inter Time x Med ter Dim 2	0.014[-0.059;0.087]	0.49
	Inter Time x upp ter Dim 2	-0.046[-0.118;0.027]	
	Inter Time x Med ter Dim 3	-0.056[-0.129;0.018]	0.22
	Inter Time x upp ter Dim 3	-0.068[-0.142;0.005]	
Life satisfaction	intercept	2.57[2.241;2.9]	
	age z-scored	-0.008[-0.046;0.03]	0.55
	gender	0.007[-0.07;0.084]	0.8
	education	0.045[-0.028;0.118]	0.72
	arms omega3	0.012[-0.094;0.119]	0.96
	arms IM	-0.008[-0.11;0.095]	
	arms ctrl	0.004[-0.098;0.106]	
	CDR status	-0.019[-0.094;0.056]	0.47
	antiepileptic	0.04[-0.205;0.285]	0.64
	antidepressant	-0.09[-0.242;0.061]	0.79
	score MMSE	0.002[-0.008;0.013]	0.52
	Time	-0.01[-0.021;0.002]	0.17
	Medium tertile Dim 1	0[-0.092;0.092]	0.95
	Upper tertile Dim 1	-0.009[-0.104;0.086]	
	Medium tertile Dim 2	-0.03[-0.119;0.059]	0.16
	Upper tertile Dim 2	0.03[-0.06;0.121]	
	Medium tertile Dim 3	0.007[-0.083;0.098]	0.95
	Upper tertile Dim 3	0.003[-0.094;0.1]	
	Inter Time x Med ter Dim 1	0.005[-0.024;0.034]	0.54
	Inter Time x upp ter Dim 1	0.012[-0.018;0.041]	
	Inter Time x Med ter Dim 2	0.016[-0.013;0.044]	0.51
	Inter Time x upp ter Dim 2	0.024[-0.003;0.054]	
	Inter Time x Med ter Dim 3	0.026[-0.003;0.054]	0.08
	Inter Time x upp ter Dim 3	0.029[0.001;0.057]	
Apathy	intercept	1.468[0.91;2.025]	
	age z-scored	0.064[0.011;0.117]	0.005
	gender	-0.004[-0.111;0.102]	0.91

Outcomes	Variables	M3 betas [95%IC]	M3 p-value (LRT)
	education	-0.033[-0.134;0.068]	0.35
	arms omega3	-0.008[-0.155;0.139]	0.94
	arms IM	-0.026[-0.167;0.116]	
	arms ctrl	0.002[-0.138;0.143]	
	CDR status	-0.004[-0.107;0.1]	0.92
	antiepileptic	-0.038[-0.378;0.301]	0.74
	antidepressant	0.24[0.031;0.449]	0.01
	score MMSE	-0.009[-0.027;0.01]	0.19
	Time	0.033[0.012;0.053]	0.02
	Medium tertile Dim 1	-0.012[-0.133;0.11]	0.95
	Upper tertile Dim 1	-0.001[-0.126;0.124]	
	Medium tertile Dim 2	0.01[-0.113;0.132]	0.91
	Upper tertile Dim 2	-0.008[-0.133;0.116]	
	Medium tertile Dim 3	-0.075[-0.2;0.049]	0.72
	Upper tertile Dim 3	-0.096[-0.223;0.03]	
	Inter Time x Med ter Dim 1	-0.029[-0.082;0.024]	0.16
	Inter Time x upp ter Dim 1	-0.034[-0.087;0.019]	
	Inter Time x Med ter Dim 2	-0.016[-0.068;0.037]	0.62
	Inter Time x upp ter Dim 2	-0.017[-0.069;0.036]	
	Inter Time x Med ter Dim 3	-0.022[-0.074;0.029]	0.25
	Inter Time x upp ter Dim 3	-0.03[-0.082;0.022]	
Self-esteem	intercept	2.074[1.798;2.35]	
	age z-scored	-0.01[-0.035;0.015]	0.27
	gender	-0.027[-0.078;0.024]	0.13
	education	0.03[-0.018;0.079]	0.66
	arms omega3	0.015[-0.055;0.085]	0.88
	arms IM	-0.001[-0.069;0.066]	
	arms ctrl	-0.003[-0.07;0.065]	
	CDR status	-0.036[-0.086;0.013]	0.33
	antiepileptic	0.056[-0.106;0.219]	0.32
	antidepressant	-0.116[-0.216;-0.016]	0.009
	score MMSE	0.01[0;0.019]	0.03
	Time	-0.011[-0.022;-0.001]	0.03
	Medium tertile Dim 1	-0.029[-0.089;0.032]	0.39
	Upper tertile Dim 1	-0.022[-0.084;0.041]	
	Medium tertile Dim 2	0[-0.059;0.059]	0.61
	Upper tertile Dim 2	0.018[-0.042;0.078]	
	Medium tertile Dim 3	0.037[-0.023;0.097]	0.16
	Upper tertile Dim 3	0.034[-0.026;0.095]	
	Inter Time x Med ter Dim 1	0.001[-0.025;0.028]	0.56
	Inter Time x upp ter Dim 1	-0.008[-0.035;0.018]	
	Inter Time x Med ter Dim 2	0.009[-0.016;0.035]	0.1
	Inter Time x upp ter Dim 2	0.027[0.001;0.053]	
	Inter Time x Med ter Dim 3	0.031[0.005;0.057]	0.01
	Inter Time x upp ter Dim 3	0.028[0.002;0.054]	
Level of anxiety	intercept	1.146[0.687;1.606]	
	age z-scored	0.016[-0.028;0.06]	0.29
	gender	-0.051[-0.14;0.038]	0.1
	education	-0.001[-0.086;0.084]	0.98
	arms omega3	-0.011[-0.134;0.111]	0.97
	arms IM	-0.017[-0.135;0.101]	
	arms ctrl	-0.018[-0.136;0.099]	
	CDR status	0.082[-0.004;0.169]	0.06
	antiepileptic	0.099[-0.184;0.383]	0.32
	antidepressant	0.021[-0.154;0.195]	0.73
	score MMSE	0.009[-0.006;0.024]	0.11
	Time	0.005[-0.012;0.022]	0.41
	Medium tertile Dim 1	0.027[-0.08;0.134]	0.57

Outcomes	Variables	M3 betas [95%IC]	M3 p-value (LRT)
	Upper tertile Dim 1	0.04[-0.069;0.149]	
	Medium tertile Dim 2	-0.01[-0.117;0.096]	0.65
	Upper tertile Dim 2	-0.035[-0.143;0.074]	
	Medium tertile Dim 3	-0.083[-0.188;0.022]	0.71
	Upper tertile Dim 3	-0.043[-0.15;0.064]	
	Inter Time x Med ter Dim 1	0.038[-0.005;0.081]	0.38
	Inter Time x upp ter Dim 1	0.028[-0.016;0.071]	
	Inter Time x Med ter Dim 2	0.047[0.004;0.091]	0.005
	Inter Time x upp ter Dim 2	-0.008[-0.051;0.035]	
	Inter Time x Med ter Dim 3	-0.002[-0.052;0.034]	0.59
	Inter Time x upp ter Dim 3	-0.015[-0.045;0.04]	

Abbreviations: GDS: Geriatric Depression scale -15 item; Dim 2: amyloid regional dimension 2 (pontine region): Dim 3: amyloid regional dimension 3 (hippocampus and bilateral caudate nuclei); med ter: medium tercile; upp ter: upper tercile