Depressive Symptoms and Amyloid Pathology

Depressive symptoms and amyloid pathology: findings from the Amyloid Biomarker Study

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Key Points

Question (1 sentence): What is the association between depressive symptoms and amyloid pathology in elderly individuals without dementia?

Findings (1-2 sentences): In this pooled analysis of 49 cohorts that included 12,769 participants, we found that the presence of depressive symptoms was not associated with amyloid pathology in participants with normal cognition but was associated with a lower frequency of amyloid pathology in participants with MCI.

Meaning (1 sentence): Mechanisms other than amyloid accumulation may commonly underly depressive symptomatology in later life.

Abstract

Importance: Depressive symptoms are associated with cognitive decline in the elderly population. Uncertainty about underlying mechanisms hampers diagnostic and therapeutic efforts.

Objective: The aim of this study was to examine the association between depressive symptoms and amyloid pathology and its dependency on sex, education and *APOE* genotype in individuals without dementia.

Design: Cross-sectional analyses were performed using data from the Amyloid Biomarker Study data pooling initiative.

Setting: Data from 49 research studies, population-based studies and memory clinics was pooled and harmonized.

Participants: We included 9,746 individuals with normal cognition (NC) and 3,023 participants with MCI for whom data on amyloid biomarkers, presence of depressive symptoms, age, sex, and cognitive status was available.

Exposures: NA

Main outcome(s) and measures(s): Aβ1-42 levels in CSF or amyloid PET scans were used to determine presence or absence of amyloid pathology. Presence of depressive symptoms was determined on the basis of scores on validated depression rating scales, evidence of a current clinical diagnosis of depression or self-reported experience of depressive symptoms.

Results:
The mean age of participants with NC was 69 years (58% female, 34% *APOE* ε4 carrier, 9.6% depressive symptoms, 27% amyloid pathology). The mean age of MCI participants was 70 years (49% female, 45% *APOE* ε4 carrier, 27% depressive symptoms, 56% amyloid pathology). In NC, the presence of depressive symptoms was not associated with amyloid pathology (OR = 1.1, 95%CI 0.90-1.40, p=0.29)**.** In MCI, the presence of depressive symptoms was associated with a lower likelihood of amyloid pathology (OR = 0.73, 95%CI 0.61-0.89, p = 0.001). When considering subgroup effects, we found that, in NC, presence of depressive symptoms was associated with a higher frequency of amyloid pathology in *APOE* ε4 non-carriers (mean difference 5.0%, 95%CI 1.0-9.0%, p = 0.022), but not in carriers.

Conclusion and relevance: Depressive symptoms were not consistently associated with amyloid pathology in persons with NC and were associated with a lower likelihood amyloid of pathology in MCI participants. These findings indicate that mechanisms other than amyloid accumulation may commonly underly depressive symptoms in late life.

Background

Depressive symptoms in the elderly are associated with future cognitive decline[1,2]. However, uncertainty about the exact causal direction and mechanisms hampers diagnostic and therapeutic efforts.

Much research has focused on examining the association between late-life depressive symptoms and amyloid pathology in relation to cognitive decline[3–5]. On the one hand, evidence exists for depressive symptoms as prodromal manifestations of neurodegeneration[4,6]. On the other hand, affective disorders, particularly more severe types such as major depressive disorder (MDD), may be an independent risk factor for cognitive decline[5,7,8]. In addition, cognitive decline and depressive symptoms share common risk factors[9], raising the possibility of overlap without a direct causal relationship. Lastly, other findings suggest that late-life depression may be primarily mediated by non-amyloid pathology[10] or pathologies other than incipient AD[11,12].

Heterogeneity in study design and populations, differences in severity of depressive complaints/diagnosis studied and biomarker modality utilized largely precludes the drawing of general conclusions[13]. Another source of heterogeneity in published research concerns the possible effects of the major genetic risk factor for sporadic Alzheimer's disease (AD) and the formation of brain amyloid plaques: the *APOE* ε4-allele. [14,15].

A better understanding of the association between depressive symptoms and amyloid pathology in elderly people without dementia is essential for further therapeutic research[16] and will aid diagnosis and prognosis in clinical settings. Therefore, the aim of the present study was to investigate the association between depressive symptoms and amyloid pathology and its dependence on age, sex, education and *APOE* ε4 carrier status in participants with normal cognition (NC) or mild cognitive impairment (MCI) included in the Amyloid Biomarker Study.

Methods

Participants

Participants for this cross-sectional study were selected from the Amyloid Biomarker Study, a data pooling initiative aiming to collate data from studies reporting information on positron-emission tomography (PET) or cerebrospinal fluid (CSF) amyloid markers[17,18]. For the current study, we selected all participants without dementia for whom data on amyloid biomarkers, age, and presence of depressive symptoms was available, leading to the inclusion of 12,769 participants from 49 centres (cohort characteristics described in **TABLE S1**). 9746 participants had NC as defined by normal scores on cognitive tests and/or absence of cognitive complaints. 3023 participants had MCI[19,20,21]. We did not investigate Subjective Cognitive Decline (SCD)[22] as a separate entity in this study.

Amyloid pathology

Following procedures described previously, Aβ1-42 levels in CSF or amyloid PET scans were used to determine presence or absence of amyloid pathology[23].Data-driven cut-offs from Gaussian Mixed Modelling (GMM) were applied to dichotomize data for 3775 participants (3579 CSF, 196 PET) and center-specific cut-offs were used to dichotomize data for 8994 participants (2345 CSF, 6649 PET)[22]**.**

Depressive symptoms and classification

The presence of depressive symptoms was evaluated within 6 months of the amyloid assessment. Presence of depressive symptoms was operationalized in two ways, as defined below. **TABLE S2** shows an overview of the type and amount of data available per centre.

1) Dichotomous presence or absence of depressive symptoms

Participants were classified as having depressive symptoms if they (1) had a score on a validated depression rating scale indicating presence of mild, moderate or severe depressive symptoms (based on published clinical cut-offs, defined in supplemental **TABLE S3**; 11609 participants from 40 centres), (2) had a current clinical diagnosis of depression (228 participants from 7 centres) or (3) self-reported experiencing depressive symptoms (n=932 participants from 16 centres).

2) Severity of depressive symptoms based on clinical cut-off values

Based on their scores on validated depression rating scales, participants were classified as having no, mild, or moderate to severe depressive symptoms using published clinical cut-offs (defined in supplemental **TABLE S3**; rating scale data available for 11609 participants from 40 centres). Where multiple rating scale scores were available for a single participant, we chose to use data from the rating scale for which the most data was available across the Amyloid Biomarker Study population. Given the rarity of severe depression in the current sample, we chose to analyse moderate and severe depressive symptoms within a single category.

Statistical analysis

Baseline differences in demographic and clinical characteristics of those with and without amyloid pathology were assessed using ANOVA or chi-square tests for continuous and categorical variables, respectively. We used generalized estimating equations to assess the association between depressive symptoms and amyloid pathology. We assumed a logit link function for binary outcomes with an exchangeable working correlation matrix and robust variance estimators to account for within-study correlation. Analyses were performed separately in the NC and MCI groups.

We first assessed the overall association between the presence of depressive symptoms and amyloid pathology. Next, we assessed the dependency of this association on age, sex, education (years of formal schooling), *APOE* ε4 carriership and number of *APOE* ε4 alleles. In secondary analyses, we assessed the association between depressive symptom severity and amyloid pathology. Finally, we examined the possible influence of amyloid measurement modality (i.e. CSF or PET) and the type of depression rating scale used (all rating scales for which the n > 100) in post-hoc analyses. We also performed a sensitivity analysis for depressive symptom severity in which we used data-driven rather than clinical cut-offs. All analyses were corrected for age. Education was dichotomized at the mean (14 years of formal schooling).

The significance level was set at p=0.005 (two-sided) and analyses were performed using IBM SPSS statistics v27. Figures were created using R (R Core Team, 2021. Foundation for Statistical Computing, Vienna, Austria).

Results

Participant characteristics

Descriptive characteristics for persons with NC (n=9746) and MCI (n=3023) are summarized in **TABLE 1**. Of participants with NC, 58% was female, 34% was *APOE* ε4 carrier, and 27% had amyloid pathology. NC participants had a mean age of 69 and had 15 years of education on average. NC participants with amyloid pathology were more likely to be older, male, *APOE* ε4 carrier and have depressive symptoms and were also more likely to have less years of education than NC participants without amyloid pathology. Of participants with MCI, 49% was female, 45% was *APOE* ε4 carrier and 56% had amyloid pathology. MCI participants had a mean age of 70 and had 12 years of education on average. MCI participants with amyloid pathology were more likely to be older and *APOE* ε4 carrier and were less likely to have depressive symptoms and moderate to severe depressive symptoms than MCI participants without amyloid pathology.

Association between depressive symptoms and amyloid pathology

In persons with NC, the presence of depressive symptoms was not significantly associated with amyloid pathology (OR = 1.1, 95%CI 0.90-1.40, p=0.29). In MCI, the presence of depressive symptoms was associated with a lower likelihood of amyloid pathology (OR = 0.73, 95%CI 0.61-0.89, p = 0.001**; FIGURE 1A).**

In NC, there was a significant interaction of depressive symptoms with *APOE* ε4 carriership and number of *APOE* ε4 alleles. The presence of depressive symptoms was associated with a higher likelihood of amyloid pathology in *APOE* ε4 non-carriers (mean difference 5.0%, 95%CI 1.0-9.0%, p = 0.022) but not in *APOE* ε4 carriers (mean difference -1.0%, 95%CI -9.0-8.0%, p = 0.89; **FIGURE 2).** When considering number of *APOE* ε4 alleles, we likewise found that presence of depressive symptoms was associated with a higher likelihood of amyloid pathology in *APOE* ε4 non-carriers (mean difference 5.0%, 95%CI 1.0-9.0%, p = 0.019) but not in those with one (mean difference 1.0%, 95%CI -7.0-9.0%, p = 0.79) or two ε4 alleles (mean difference -12.0%, 95%CI -41.0%-18.0%, p = 0.44). In MCI, no interaction effects were found for *APOE* ε4 carrier status or number of *APOE* ε alleles.

We did not find any interactions of age, sex or education with depressive symptoms for the NC or MCI groups (p = 0.84, p = 0.13 and p = 0.65 for NC; p = 0.88, p = 0.55 and p = 0.93 for MCI, respectively).

Association between depressive symptom severity and amyloid pathology

In NC, severity of depressive symptoms was not significantly associated with amyloid pathology (p = 0.31). In MCI, severity of depressive symptoms was associated with a higher likelihood of amyloid pathology (OR = 0.79, 95%CI 0.62-1.01, p = 0.064 for mild vs. no symptoms; OR = 0.57, 95%CI 0.41-0.78, p < 0.001 for moderate to severe vs. no symptoms; OR = 0.72, 95%CI 0.50-1.03, p = 0.072 for moderate to severe vs. mild symptoms; **FIGURE 1B**). When evaluating the association between depressive symptom severity and amyloid pathology using data-driven rather than clinical cut-offs, we found a main effect of depression on amyloid pathology in NC but not in MCI. Results are detailed in the supplement.

Post hoc analyses

In NC, there was an interaction between biomarker modality and presence of depressive of symptoms. There was an association between presence of depressive symptoms and amyloid pathology measured with CSF (p-interaction 0.010, mean difference 5.0%, 95%CI 1.0-10.0%, p = 0.013) while this association did not exist when amyloid was measured using PET (mean difference -3.0%, 95%CI -7.0-1.0%, p = 0.20). In MCI, no significant interaction of biomarker modality with presence of depressive symptoms was noted.

In NC, there was an interaction between rating scale used and presence of depressive symptoms (p interaction 0.010). There was a significant difference in the prevalence of amyloid pathology between those with and without depressive symptoms if presence of depressive symptoms was measured using the Geriatric Depression Scale (GDS) 15 but not if measured by the Hospital Anxiety and Depression Scale (HADS), GDS30 or the Center for Epidemiologic Studies Depression Scale (CES-D). In MCI, there also was an interaction between rating scale used and presence of depressive symptoms (p interaction <0.001) There was a significant difference in the prevalence of amyloid pathology between those with and without depressive symptoms if presence of depressive symptoms was measured using the Brief Symptom Inventory (BSI), GDS15, Montgomery Asberg Depression Rating Scale (MADRS) and CES-D but not if measured by the GDS30.

Discussion

General findings on amyloid pathology and depressive symptoms

The present study investigated the association of depressive symptoms with amyloid pathology in participants without dementia**.** In NC, presence and severity of depressive symptoms were not consistently associated with amyloid pathology. In MCI, presence and severity of depressive symptoms were associated with a lower likelihood of amyloid pathology. When considering subgroup effects, we found that, in NC, presence of depressive symptoms was associated with a higher frequency of amyloid pathology in *APOE* ε4 non-carriers but not in carriers. Findings suggest that mechanisms other than amyloid accumulation may underly presence of depressive symptomatology in late life.

In NC, no effect of depressive symptoms on amyloid pathology was identified. However, the lack of significant effects in individuals with NC must be interpreted in the light of a relatively low burden of depressive symptoms (9.6%) in this group. Nevertheless, this finding may suggest that amyloid pathology - i.e., prodromal or preclinical AD – does not play a major role in explaining (subsyndromal or mild) depressive symptoms in older adults with normal cognitive test scores. This finding may inform further research into preclinical neurodegeneration and/or subjective cognitive decline (SCD)[24–26]. Other studies have identified the absence of depressive symptoms as a predictor of amyloid pathology in SCD, a group included under NC in this study.[25,26] This may be due to the relatively high prevalence of depressive symptoms in SCD due to causes unrelated to degenerative disease.[27]

In participants with MCI, the presence of depressive symptoms was associated with a lower likelihood of amyloid positivity. This effect was more pronounced when considering severity of symptoms, demonstrating that individuals with MCI exhibiting mild and especially moderate to severe depressive symptoms are generally less likely to exhibit amyloid pathology compared to those without depressive symptoms. This observation may indicate that depressive symptoms and disorders are not generally caused by amyloid pathology, but may themselves play an independent causal role in cognitive decline, even suggesting some dose-response relationship[3,28]. Alternatively, this association may be mediated by non-amyloid (e.g., vascular) pathologies [29–31]. Indeed, a very large autopsy study of 741 individuals[32] recently supported this hypothesis, strengthening the so-called vascular hypothesis of geriatric depression[33].

APOE, sex and education

The presence of depressive symptoms in NC was associated with an increased likelihood of amyloid pathology in *APOE* ε4 non-carriers only. Several explanations of this finding are possible. For example, it may suggest an amyloidogenic mechanism triggered by depressive symptoms[34,35] that is not seen in those already predisposed to amyloid pathology by *APOE* ε4 alleles[36], and may provide avenues for future research. None of the identified associations were dependent on sex or educational level. Compared with depressive disorders in younger adults, it remains unclear whether and how depressive disorders in aging women differ in frequency or quality from those in aging men.[37–39]

Diagnostic modality, rating scale effects and use of data-driven rather than clinical cut-offs

In NC participants, depressive symptoms were associated with amyloid pathology only if assessed by CSF (n=5924) rather than PET (n=6845).This may be due to an intrinsic characteristic of CSF amyloid markers to diagnose amyloid abnormalities earlier than nuclear imaging techniques do[40,41] Alternatively, it could reflect an independent pathophysiological signal[42–44] linking the soluble form of Aβ1-42 in CSF as opposed to the more static, fibrillary amyloid protein measured by PET, with low-grade depressive symptoms. [45]

In both NC and MCI, the association between presence of depressive symptoms and amyloid pathology was dependent on the rating scale used. One possible explanation may be that the depression scales included measure different aspects of the depressive symptom spectrum and that these may be differentially related to amyloid pathology[46,47]. Some of the rating scales used may also be more tailored to the specific population included in the study than others. For example, the GDS-15 may be more sensitive to symptoms of depression that are specifically related to cognitive impairment, or more prevalent in the aging population in general.[48] The differential result for the GDS15 and 30 in MCI is perhaps the most striking, but it has been noted before that both scales are not simply a longer or shorter version of the other[55].

When we used data-driven rather than clinical cut-offs for depression severity, we found a significant association between severity of depressive symptoms and amyloid pathology in NC rather than MCI. This result is likely driven by the limited number of NC participants who have moderate to severe depressive symptoms when assessed using clinical cut-offs. However, this finding does imply that, in participants with NC, use of routine clinical cut-offs may not identify levels of depressive symptomatology that could be noteworthy in the light of risk for future pathology or decline.

Conclusion

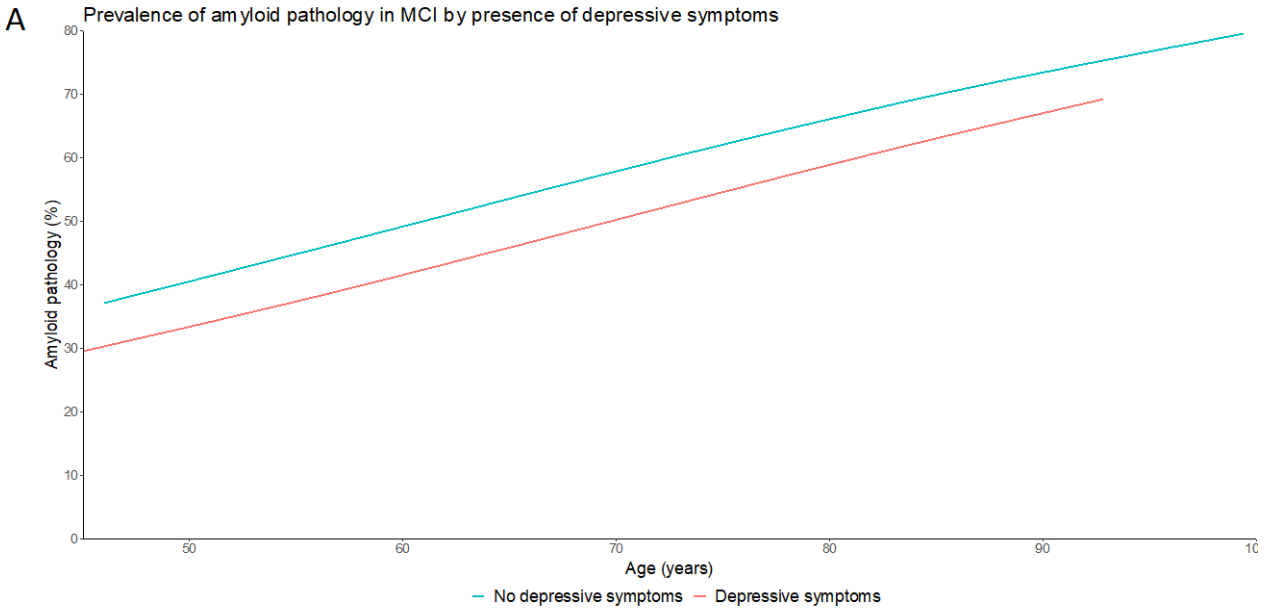
Overall, depressive symptoms are not consistently related to amyloid pathology in normal cognition, although possible differences by APOEε4 allele, biomarker modality and depression symptom measurement cut-offs used warrant further exploration. In participants with MCI, depressive symptoms were associated with a lower likelihood of amyloid pathology. These findings indicate that mechanisms other than amyloid accumulation may underly depressive symptoms in older adults without dementia.

Tables and figures

Table 1: Participant characteristics								
	NC				MCI			
	Total, n = 9746	No Amyloid pathology, n = 7098	Amyloid pathology, n = 2648	P-value group comparison	Total, n = 3023	No Amyloid pathology, n = 1335	Amyloid pathology, n = 1688	P-value group comparison
Age, mean (SD)	68.6 (8.9)	67.8 (9.0)	70.6 (8.3)	P < 0.001	70.2 (8.7)	68.7 (9.1)	71.5 (8.2)	P < 0.001
Female, n(%)	5664 (58.2%)	4170 (58.7%)	1494 (56.6%)	P = 0.032	1481 (49.0%)	658 (49.3%)	823 (48.8%)	P = 0.77
Education years, mean (SD)	15.2 (3.8)	15.2 (3.8)	15.0 (3.9)	P = 0.002	11.8 (4.5)	11.7 (4.4)	12.0 (4.6)	0.10
APOE ε4 carrier, n(%)	3002 (34.0%)	1686 (26.1%)	1316 (56.0%)	P < 0.001	1046 (34.6%)	243 (24.3%)	803 (60.2%)	P < 0.001
Missing, n(%)	923 (9.5%)	627 (8.8%)	296 (11.2%)		689 (22.8%)	335 (25.1%)	354 (21.0%)	
Presence of depressive symptoms, n(%)	937 (9.6%)	649 (9.1%)	288 (10.9%)	P = 0.01	824 (27.3%)	428 (31.1%)	396 (23.5%)	P < 0.001
Symptom severity								
No depressive	8549 (91.1%)	6290 (91.5%)	2259 (90.2%)	P = 0.16	1696 (76.1%)	694 (71.3%)	1002 (79.8%)	P < 0.001

symptoms, n(%)								
Mild depressive symptoms, n(%)	711 (7.6%)	500 (7.3%)	211 (8.4%)		424 (19.0%)	211 (21.7%)	213 (17.0%)	
Moderate to severe symptoms, n(%)	120 (1.3%)	86 (1.3%)	34 (1.4%)		109 (4.9%)	69 (7.1%)	40 (3.2%)	
Missing, n(%)	366 (3.8%)	222 (3.1%)	144 (5.4%)		794 (26.3%)	361 (27.0%)	433 (25.7%)	

Figure 1A & B: Prevalence of amyloid pathology by presence and severity of depressive symptoms



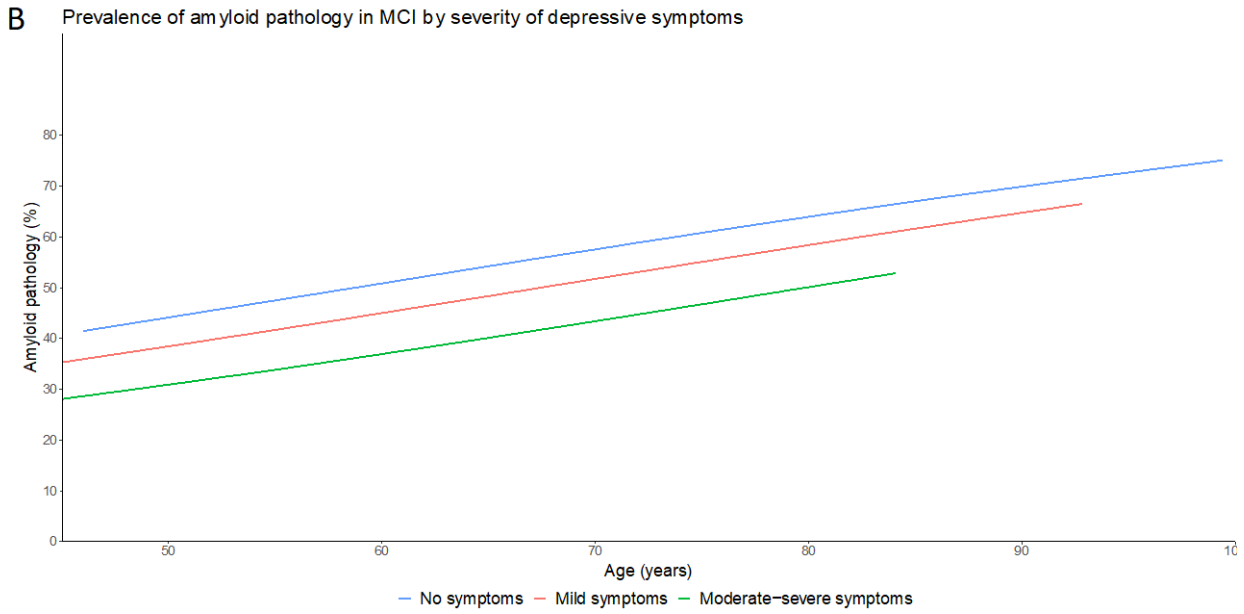
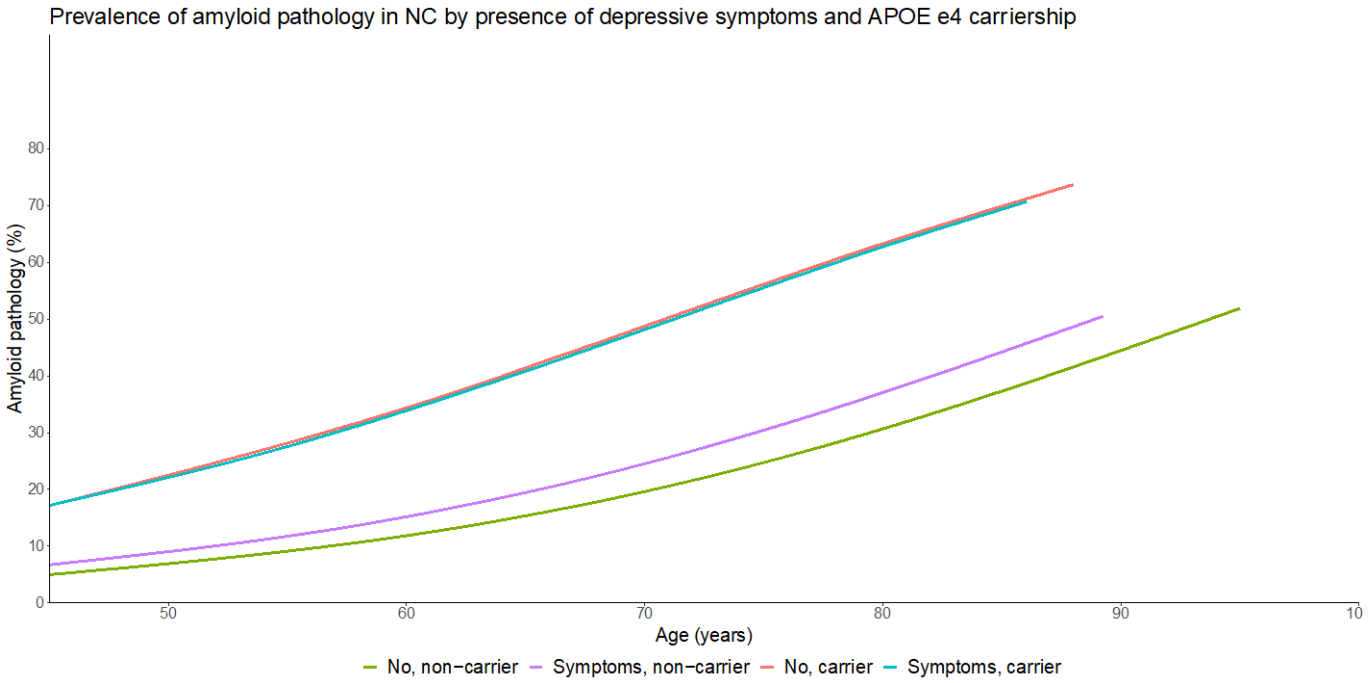


Figure 2: Prevalence of amyloid pathology by presence of depressive symptoms and *APOE* ε4 carrier status



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*****Data used in preparation of the present article were obtained from the ADNI database (adni.loni.usc.edu). As such, ADNI investigators provided and contributed to the design and implementation of the ADNI data but did not participate in the analysis or writing of this article. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_ List.pdf. The ADNI was launched in 2003 as a public-private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI is to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer disease. Data collection and sharing for this project was funded by grant U01 AG024904 from the NIH and award W81XWH-12-2-0012 from the US Department of Defense. The ADNI is funded by the NIA; the National Institute of Biomedical Imaging and Bioengineering; and AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica Inc, Biogen, Bristol-Myers Squibb Company, CereSpir Inc, Cogstate, Eisai Inc, Elan Pharmaceuticals Inc, Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc, Fujirebio, GE Healthcare, IXICO Ltd, Janssen Alzheimer Immunotherapy Research and Development LLC, Johnson & Johnson Pharmaceutical Research and Development LLC, Lumosity, Lundbeck, Merck & Co Inc, Meso Scale Diagnostics LLC, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc, Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research provides support to the ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the NIH (www. fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California. The ADNI data are disseminated by the Laboratory for Neuroimaging at the University of Southern California.

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Dr Alcolea reported participating in advisory boards from Fujirebio-Europe and Roche Diagnostics; receiving speaker honoraria from Fujirebio-Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica SL, Zambon SAU, and Esteve Pharmaceuticals SA; and filing a patent application (WO2019175379 A1 Markers of Synaptopathy in Neurodegenerative Disease).

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Dr Hort has consulted Eisai, Biogen, Eli Lilly, Roche and Neurona lab and holds stock options in Alzheon company.

Dr Eckerström reported being employed as an independent reviewer at Medavante-Prophase.

Dr Engelborghs reported participating in consultancy or on advisory boards of Biogen, Danone, Eisai Inc, Icometrix, Pfizer, Novartis, and Roche, and receiving unrestricted research grants (paid to his institution) from ADx Neurosciences and Janssen Pharmaceuticals.

Dr Grimmer reported receiving consulting fees from AbbVie, Alector, Anavex, Biogen, Cogthera, Eli Lilly, Functional Neuromodulation, Grifols, Iqvia, Janssen, Noselab, Novo Nordisk, NuiCare, Orphanzyme, Roche Diagnostics, Roche Pharma, UCB, and Vivoryon; lecture fees from Biogen, Eisai, Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, Schwabe, and Synlab; and has received grants to his institution from Biogen, Eisai, and Roche Diagnostics.

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Dr Scheltens is a full time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. He has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation he was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. He is past chair of the EU steering committee of the phase 2b program of Vivoryon and

the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

Dr Snyder reported being a consultant to Alzheon Inc, AlzeCure Pharma, and AlzPATH Inc outside the submitted work.

Dr Soininen reported receiving personal consultation fees from AC Immune and Novo Nordisk outside the submitted work.

Dr Sperling reported receiving honorarium for consulting from AC Immune, Acumen, Alnylam, Cytox, Genentech, Janssen, JOMDD, Oligomerix, Neuraly, Neurocentria, Renew, Prothena, and Shionogi; reported receiving research funding from the National Institute on Aging (NIA), Alzheimer's Association, Eisai Inc, Eli Lilly and Company, and Janssen; and reported the following financial relationships for her spouse (Dr Keith Johnson): Cerveau, Janssen, AC Immune, and Novartis.

Dr A. Wallin reported receiving gratuity for lectures from Lundbeck.

Dr Zetterberg reported having served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

No other disclosures were reported.

Consent statement

All individual sites contributing to the Amyloid Biomarker Study have obtained local ethical approval and the Amyloid Biomarker Study was approved by the Medical Ethics Committee of the Maastricht University Medical Center which declared that the Medical Research Involving Human Subjects Act (WMO) does not apply to the study and waived the informed consent requirement because de-identified data were used.

Data sharing statement: data management system

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