Journal of Affective Disorders 368 (2025) 73–81

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Interactions between mild depressive symptoms and amyloid pathology on the trajectory of neurodegeneration, cognitive decline, and risk of Alzheimer's disease

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ARTICLE INFO

Keywords:
Mild depressive symptoms
Amyloid-β
Cognitive decline
Neurodegeneration
Alzheimer's disease

ABSTRACT

Background: Alzheimer's disease (AD) was driven by the interplay between modifiable environmental factors and β-amyloid (Aβ) pathology. We aimed to investigate the interaction effects of mild depressive symptoms (MDS) with Aβ on AD development.

Methods: Longitudinal data of 1746 non-demented adults (mean age = 73 years, female = 53 %, maximum = 10 years) were derived from the Alzheimer's Disease Neuroimaging Initiative cohort. MDS was separately defined by the baseline status, longitudinal latent class, and average intensity during follow-up. Amyloid-positive (A+) status was determined based on cerebrospinal fluid levels of β-amyloid. Regression models were employed to analyze the interactive effects of MDS with A+ on cognitive decline, neurodegeneration, and AD incidence.

Results: Individuals with both A+ status and MDS at baseline experienced the fastest neurodegeneration ($p < 0.01$), cognitive decline ($p < 0.05$), and a higher risk of developing AD (HR = 5.23, $p < 0.001$). Furthermore, A+ participants with the trajectory of increasing depressive symptoms demonstrated more pronounced neurodegeneration ($p < 0.001$), cognitive decline ($p < 0.01$), and elevated risk of AD (HR = 10.45, $p < 0.001$). Finally, A+ status in combination with a higher average intensity of depressive symptoms was associated with faster brain atrophy ($p < 0.01$) and brain metabolism decline ($p < 0.05$), cognitive decline (p < 0.05), and higher AD risk (HR = 13.99, $p < 0.001$).

Conclusion: These findings emphasized that the MDS-Aβ interaction relationship should be considered in risk stratification, prediction, and early management of neurodegeneration and cognitive decline in the pre-dementia stage.

1. Introduction

Alzheimer's disease (AD), the main cause of dementia, is rapidly becoming one of the most expensive and highly disabling disease burdens in this century (Scheltens et al., 2021). Amyloid-β pathology, a characteristic feature of AD, may precede clinical symptoms of the disease by approximately 15 to 20 years (Jack Jr. et al., 2013; Jia et al., 2024). Lines of evidence have revealed important roles of interactions between modifiable environmental factors and amyloid pathology in promoting AD occurrence (Xu et al., 2021a; Tissot et al., 2021). As common NPSs in older adults without dementia, depressive symptoms have long been regarded as one of key modifiable risk factors associated with AD, and studies have shown a correlation between amyloid-β deposition and depressive symptoms (Tissot et al., 2021; Twait et al., 2024; Lewis et al., 2022). We previously reported that mild depressive symptoms (MDS) (Byers et al., 2012; Kaup et al., 2016; Al Mheid et al., 2016), a common yet often overlooked subclinical status, was linked to poorer global cognition and an 83 % increased risk of developing AD

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[1] The two authors contributed to the present work equally.
[2] The data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. 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.

https://doi.org/10.1016/j.jad.2024.08.235
Received 12 May 2024; Received in revised form 24 August 2024; Accepted 31 August 2024
Available online 10 September 2024

dementia. Furthermore, we observed that MDS predicted higher cerebral amyloid burden, which could mediate the relationship of MDS with impaired cognition (Xu et al., 2021b). It can be thus reasonably postulated that a potential interaction might exist between MDS and amyloid pathology which might modulate the risk of AD occurrence. However, little is known about these interaction effects.

Another key limitation is that majorities of longitudinal studies examining the relationships of depression with dementia tended to quantify the depressive symptoms at a single time point. This study design cannot capture the nature of individual variability and average exposure dose during follow-up, leading to grouping bias and misjudgment of the true associations (Cui et al., 2008). Otherwise, depicting trajectory and dynamic features improved capabilities in capturing long-term exposure and individual variations, facilitating a better understanding of etiological correlations. Moreover, trajectory methods can pinpoint early distinct adverse trajectories as potential targets for intervention (Lennon et al., 2018). Herein, we aimed to investigate whether MDS, defined by baseline status, trajectory group, and average intensity of depressive symptoms during follow-up, could interact with amyloid pathology to impact neurodegeneration, cognitive decline, and AD risk using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Methods

2.1. Participants

Longitudinal data of 2084 adults were downloaded from the ADNI database (adni.loni.usc.edu). The primary goal of ADNI is to identify the optimal combinations of serial MRI, PET, and other biological markers, in conjunction with clinical and neuropsychological assessments to predict and measure the progression of mild cognitive impairment (MCI) and early AD (Cummings, 2010; Weiner et al., 2015; Moon et al., 2017). The participants are volunteers aged 55 to 90 with normal cognition (NC), mild cognitive impairment, or mild AD (Weiner et al., 2013; Weiner et al., 2010; Trojanowski et al., 2010). At baseline, each participant underwent an in-person interview of general health and functional ability, followed by a standardized assessment including a battery of neuropsychological tests. Follow-up data were collected at sequential intervals of approximately 12 months. ADNI obtained approval from the Institutional Review Committee of all participating institutions and received written informed consent from all participants or their guardians.

In the present study, 338 individuals diagnosed with AD at baseline were removed. The analysis proceeded in three parallel phases. Firstly, 532 individuals were excluded due to a lack of cognitive domain scores, leaving 1214 individuals with Geriatric Depression Scale (GDS) scores to verify the interaction between baseline MDS and amyloid. Secondly, due to insufficient data needed to evaluate the depressive symptom trajectory, 1262 individuals were excluded, leaving 584 individuals who had GDS scores at baseline, year 1, year 2, and year 3 to verify the interaction between depressive symptom trajectory and amyloid. Thirdly, due to the lack of GDS scores during the follow-up period, 528 individuals were excluded. Ultimately, 1218 individuals had GDS scores during the follow-up period. These individuals were all included in the initial sample and underwent data cleaning and filtering (Fig. 1A).

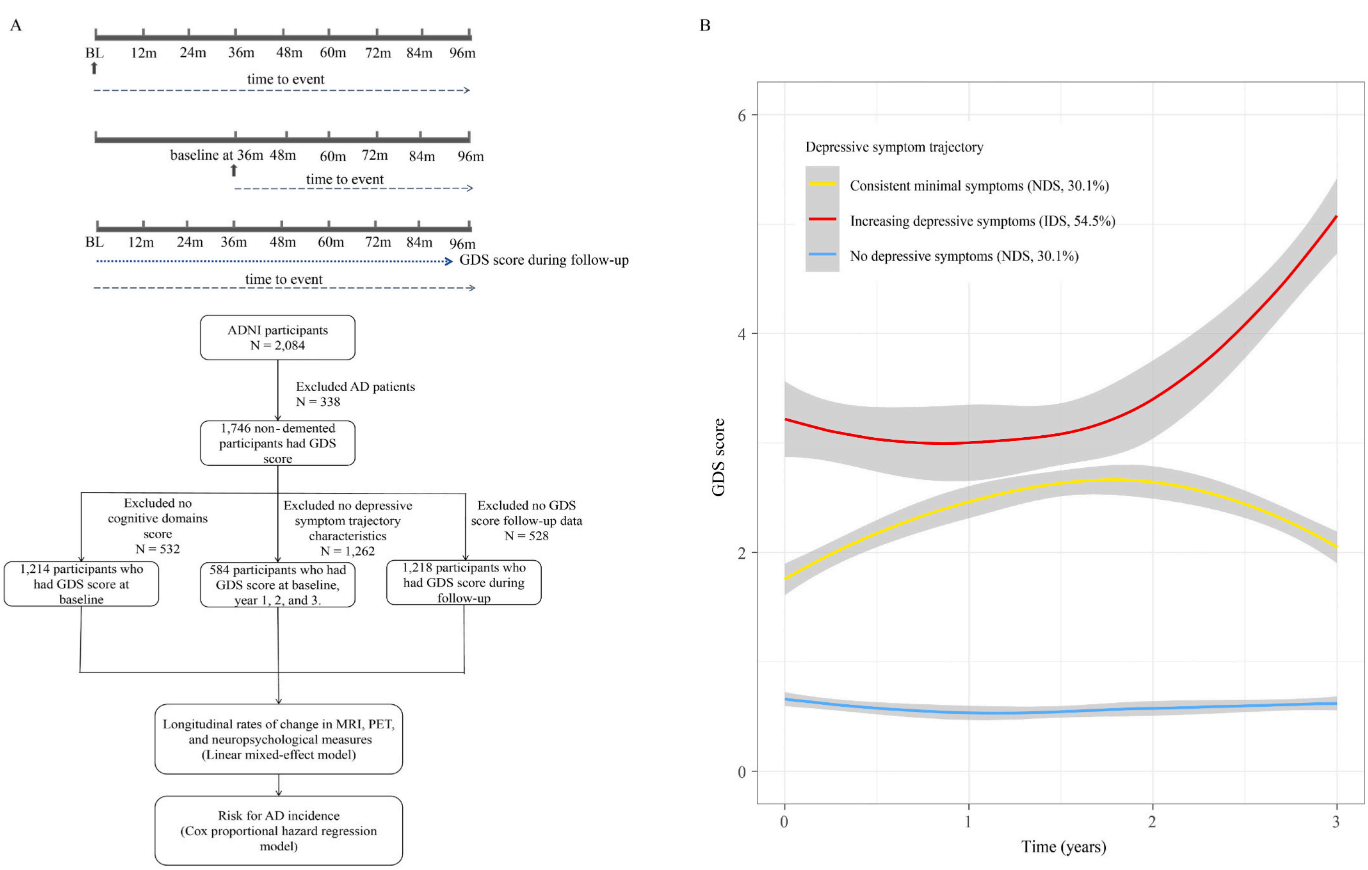

Fig. 1. Flowchart of study design.

1A. The research overview summarizes the selection and analysis process of the population. 1B. Groups of depressive symptom trajectory.

Abbreviations: ADNI: Alzheimer's Disease Neuroimaging Initiative; GDS, Geriatric Depression Scale; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography. NDS: no depressive symptoms; CMS: consistent minimal symptoms; IDS: increasing depressive symptoms.

2.2. Definition of mild depressive symptoms

GDS was employed to assess depressive symptoms at baseline and the subsequent follow-up visits (Shin et al., 2019). Participants with GDS scores over 7 were excluded from the present study to ensure that the exposure group was representative of MDS. Three approaches were used to define MDS. First, baseline MDS were defined by a GDS score of ≥1 and ≤7, by previous publications (Xu et al., 2021c). Second, trajectories of depressive symptoms over the first 3 years were grouped using the latent class growth curve analysis, a semiparametric analysis that differentiates groups of individuals based on their probability of following a similar trajectory on an outcome over time (Jones et al., 2001). Specifically, the "lcmm" package in R software was used to estimate trajectories of depressive symptoms across four visits (baseline, years 1, year 2, and year 3) following the recommended procedures (Andruff et al., 2009). Each trajectory group had to include at least 5 % of participants. We selected an optimal model structure using the lowest Bayesian information criteria (BIC) value and satisfactory values from the model adequacy assessments. An average of these maximum posterior probabilities of assignments (APPA) above 70 %, in all classes, is regarded as acceptable. These procedures indicated that a model with 3 trajectories was superior to other models (BIC = 11,179). Although a model with 5 trajectories was associated with further improvement in Model fit (BIC for 5-trajectory model = 11,060; BIC for 4-trajectory model = 11,073), these models yielded trajectories with <5 % of participants. Therefore, we selected the 3-trajectory model for use in subsequent analyses. A total of 538 participants were classified into three groups: always no depressive symptoms (NDS, 30.1 %), consistent minimal depressive symptoms (CMS, 15.4 %), and increasing depressive symptoms (IDS, 54.5 %) (Fig. 1B). Third, we calculated the mean exposure intensity of MDS, calculated by cumulative GDS scores divided by the total follow-up years before dementia diagnosis (Fig. 1A). The lowest tertile of the intensity was regarded as the low-burden group, whereas the rest was labeled as the high-burden group.

2.3. Aβ and p-tau status determination

CSF procedural protocols have been described previously (Shaw et al., 2009). We applied the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework to characterize the biomarker profile of each participant. Each biomarker was dichotomized into positive (+) and negative (−) groups based on established cutoff values. Participants with CSF $A\beta_{1-42}$ concentration < 976.6 pg/ml and CSF p-tau_{181} concentration > 21.8 pg/ml as measured by Elecsys were considered A positive (A+) and T positive (T+), respectively. The CSF biomarker status established by the cutoff was shown to be highly consistent with PET classification (Hansson et al., 2018).

2.4. Covariate measurements

The covariates included in the basic models were age, gender, years of education (continuous variable), cognitive status (mild cognitive impairment [MCI] versus normal cognition [NC]), and *APOE* ε4 status. *APOE* allele is the most significant genetic risk factor for sporadic AD (Giannouli and Tsolaki, 2021), rs7412 and rs429358 were genotyped separately to define the *APOE* ε2/ε3/ε4 isoforms (Kim et al., 2011). Furthermore, other confounders were confirmed by screening the medical history, including hyperlipidemia (yes or no), hypertension (yes or no), insomnia (yes or no), diabetes (yes or no), stroke history (yes or no), depression history (yes or no), and current smoking status (yes or no).

2.5. Cognitive measurements and AD diagnosis

Cognitive functions were measured at baseline and sequential intervals of approximately 12 months. Global cognitive function was tested by the scores of the Alzheimer's Disease Assessment Scale (ADAS) (Kueper et al., 2018). Comprehensive scores for executive and memory functions were constructed and validated based on the neuropsychological batteries (Crane et al., 2012; Gibbons et al., 2012). In brief, the indicators of executive functions include Category Fluency, WAIS-R Digit Symbol, Trails A & B, Digit Span Backwards, and clock drawing. The indicators of memory function include relevant items of the Rey Auditory Verbal Learning Test (RAVLT), ADAS-Cog, Logical Memory, and Mini-Mental State Examination (MMSE). MCI diagnoses were based on subjective memory complaints, abnormal memory performance on the Wechsler Memory Scale-Revised (WMS-R), an MMSE score between 24 and 30, a Clinical Dementia Rating (CDR) of 0.5, with a Memory Box score of at least 0.5, and cognitive and functional abilities remained sufficiently preserved to rule out a diagnosis of AD. In contrast, ADNI classifies CN participants as those with no memory complaints, normal memory performance on the WMS-R (above education-adjusted cutoffs), an MMSE score between 24 and 30, a CDR of 0, and no significant cognitive or functional impairment (Edmonds et al., 2019). The NIA-AA criteria were used for the diagnosis of probable AD (Jack Jr. et al., 2018).

2.6. Neurodegeneration assessment by FDG PET and MRI

Brain metabolism levels were estimated using [18F] florbetapir PET. Summary florbetapir standard uptake value ratios were acquired by averaging uptake ratios across cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal regions) normalized by the reference region (whole cerebellum). FDG-PET was utilized to identify significant hypometabolic regions (metaROIs) linked to AD's pathological metabolic changes. The pre-defined regions of interest were determined based on a literature review, which included angular, temporal, and posterior cingulate regions. The mean of the provided metaROIs was normalized by dividing it by the mean of the top 50 % of the pons/vermis reference region (Landau et al., 2011; Landau et al., 2010).

The scan data was collected on 1.5 T GE, Philips, and Siemens MRI scanners using a magnetization-prepared rapid acquisition gradient echo sequence, which was selected and tested by the ADNI Consortium's MRI core. Brain volume was computed using FreeSurfer, an automated segmentation and reconstruction software package, which processes the T1-weighted images to segment various brain regions, including the cortex, hippocampus, amygdala, and ventricles. The total brain volume was calculated by summing the volumes of all segmented brain regions (Jack Jr. et al., 2008). Two high-resolution T1-weighted MRI scans were collected for each participant using a sagittal 3D MP-RAGE sequence with approximate TR = 2400 ms, minimum full TE, approximate TI = 1000 ms, and approximate flip angle of 8 degrees. Scans were collected with a 24 cm field of view and an acquisition matrix of 192 × 192 × 166 (x, y, z dimensions), to yield a standard voxel size of 1.25 × 1.25 × 1.2 mm. Images were then reconstructed to give a 256 × 256 × 166 matrix and voxel size of approximately 1 × 1 × 1.2 mm (Risacher et al., 2009).

2.7. Statistical analyses

First, we used the chi-squared test (χ^2) for categorical variables and one-way analysis of variance (ANOVA) for continuous variables to examine the group differences of baseline characteristics. The "car" package in R software (version 4.3.1) was employed to normalize the dependent variables in the regression models.

Second, the linear mixed-effects models (LME) regression analyses were conducted in R (version 4.3.1) using the "lme4" package to examine whether MDS (baseline levels, trajectory group, and mean intensity) could modulate the relationships of Aβ with changes of neural degenerative imaging markers and cognitive decline. The LME models were used because they could handle unbalanced and censored data as well as a continuous variable for time (Gibbons et al., 2010). Outcome variables were brain metabolism, brain structure, and cognitive functions. The LME models had random intercepts and slopes nested within participants and an unstructured covariance matrix for the random effects. Fixed effects included main effects of baseline Aβ status (time-invariant), MDS (baseline levels, trajectory group, and mean intensity of depressive symptoms assessed by the GDS), years of follow-up (time-varying variable, hereinafter referred to as "VISCODE"), two-way interaction terms of MDS × Aβ status, VISCODE × MDS, and VISCODE × Aβ status, as well as three-way interaction terms of VISCODE × MDS × Aβ status. The overall significance of the three-way interaction term was assessed by the likelihood ratio tests comparing the full model and a nested model that did not include the three-way interaction term. Regression diagnostics were conducted and twelve outliers that were situated outside ±3 standard deviation (SD) were excluded to indicate that all models met the necessary assumptions: model residuals appeared normally distributed and did not exhibit heteroscedasticity. Finally, a statistical comparison of model coefficients was performed using the Wald test via the "aod" package to determine the group difference.

Finally, the time-dependent Cox proportional hazards regression models were used to assess whether the synergistic effect of Aβ with MDS was associated with the risk of incident AD. The "cox. zph" function is used to test the proportional risk hypothesis. Individuals who were lost to follow-up were censored during their last evaluation. Risk estimates were expressed as hazard ratios (HR) and 95 % confidence intervals (CI). The "survival," "survminer," "ggpubr," "ggplot2," "survival", and "magrittr" packages in R version 4.3.1 software were used to conduct the above analyses.

R software version 4.3.1 (packages including "nlme" and "ggplot2") was used for statistical analyses and figure preparation. $P < 0.05$ was considered significant except where specifically noted. All analyses were adjusted for age, gender, educational level, *APOE* ε4, and cognitive diagnosis of MCI. As for the analyses of brain structures, the intracranial volume (ICV, continuous variable) was added in the model. Sensitivity analyses were conducted by adding additional covariates, including hyperlipidemia, hypertension, insomnia, diabetes, stroke history, and current smoking status.

3. Results

3.1. Synergistic effects of baseline MDS with A status on neurodegeneration and cognitive decline

A total of 1214 non-demented individuals (mean age = 72.5 years, education years = 16.2, female = 52.0 %) were included to investigate the interaction of baseline MDS with A status. Among the participants, 34.4 % were amyloid-positive individuals with MDS. Compared to individuals with only amyloid-positive or only MDS, those who were amyloid-positive with MDS tended to have lower levels of education ($p = 0.0002$) and a higher proportion of MCI ($p < 0.0001$) (Table 1).

The likelihood ratio tests comparing full and nested LME models indicated that the three-way interaction of MDS × A status × VISCODE accounted for a statistically significant amount of variance in imaging neurodegeneration ($p = 0.0075$ for FDG-PTE, $p = 0.0038$ for hippocampus, $p = 0.0051$ for entorhinal cortex, and $p = 0.0002$ for mid-temporal cortex) and cognitive performance ($p = 0.0038$ for general cognition, $p = 0.0386$ for memory function, and $p = 0.0008$ for executive function). The rates of neurodegeneration and cognitive changes for each group were separately calculated from model coefficients and greater rates of decline were observed in the A+ group with MDS, compared with other groups (Table 2). MDS predicted greater neurodegeneration and cognitive decline in the A+ group, but not in the A− group ($p = 0.002$ for general cognition and $p < 0.001$ for executive function; $p < 0.001$ for hippocampus, $p = 0.008$ for entorhinal cortex, and $p = 0.008$ for mid-temporal cortex). The above-mentioned primary results were barely changed after adding additional covariates.

Table 1
Population characteristics at baseline.

Characteristics	Total ($N = 1214$)	A−/No-MDS ($N = 252$)	A−/MDS ($N = 366$)	A+/No-MDS ($N = 178$)	A+/MDS ($N = 418$)	*p*-Value
1. Demographic information						
Age, Years, mean ± sd	72.5 ± 7.1	72.1 ± 6.2	71.5 ± 7.7	75.0 ± 6.6	72.6 ± 7.0	<0.0001
Female, n (%)	631 (52.0)	116 (9.6)	177 (14.6)	94 (7.7)	244 (20.1)	0.0062
Education, years, mean ± sd	16.3 ± 2.6	16.6 ± 2.5	16.3 ± 2.6	16.3 ± 2.5	16.2 ± 2.8	0.0002
APOE ε4 carrier status, n (%)	499 (41.0)	54 (4.4)	81 (6.7)	106 (8.7)	258 (21.2)	0.2656
MCI, n (%)	684 (56.3)	58 (4.8)	213 (17.5)	85 (7.0)	328 (27.0)	<0.0001
Stroke, n (%)	42 (3.4)	5 (0.4)	18 (1.5)	5 (0.4)	14 (1.1)	0.2359
Current smoker, n (%)	190 (15.6)	50 (4.1)	59 (4.9)	25 (2.0)	56 (4.6)	0.1467
Insomnia, n (%)	103 (8.4)	22 (1.8)	23 (1.9)	18 (1.5)	40 (3.4)	0.3152
Hyperlipidaemia, n (%)	592 (48.7)	125 (10.3)	163 (13.4)	96 (7.9)	208 (35.1)	0.1903
Hypertension, n (%)	534 (43.9)	119 (9.8)	168 (13.8)	84 (6.9)	163 (13.4)	0.0864
Diabetes, n (%)	95 (7.8)	22 (1.8)	22 (1.8)	19 (1.6)	32 (2.6)	0.2641
GDS score, mean ± sd	1.31 ± 1.37	–	1.97 ± 1.21	–	2.06 ± 1.21	<0.0001
2. Neuropsychological assessments, mean ± sd						
ADAS score, mean ± sd	13.8 ± 7.0	10.8 ± 5.0	11.7 ± 5.5	14.7 ± 7.2	17.1 ± 7.7	<0.0001
EF score[a], mean ± sd	0.96 ± 0.67	1.21 ± 0.70	0.97 ± 0.63	0.83 ± 0.69	0.77 ± 0.59	<0.0001
MEM score[b], mean ± sd	0.88 ± 0.56	1.09 ± 0.53	0.91 ± 0.0.55	0.81 ± 0.54	0.69 ± 0.52	<0.0001
3. Imaging characteristics, mean ± sd						
Hippocampus volume[c], mm^3	6965 ± 1088	7366 ± 921	7173 ± 1110	7054 ± 1032	6608 ± 1051	<0.0001
Entorhinal volume[c], mm^3	3609 ± 711	3842 ± 667	3773 ± 705	3561 ± 696	3405 ± 678	<0.0001
Mid-temporal volume[c], mm^3	19,783 ± 2784	20,209 ± 2508	20,486 ± 2723	19,263 ± 2787	19,263 ± 2796	<0.0001
FDG-PET[d] SUVr	1.27 ± 0.08	1.30 ± 0.05	1.30 ± 0.06	1.26 ± 0.07	1.25 ± 0.08	0.0329

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; GDS, Geriatric Depression Scale; ADAS, Alzheimer's Disease Assessment Scale; EF, executive function; MEM, memory function; FDG, Fluorodeoxyglucose; MDS, mild depressive symptoms; A, β-amyloid$_{1–42}$; A+, amyloid-positive; A−, amyloid-negative.
p-value < 0.05 is considered statistically significant.

[a] No. = 876.
[b] No. = 932.
[c] No. = 393.
[d] No. = 883.

Table 2
Synergistic effects of baseline MDS with A status on neurodegeneration and cognitive performance.

Variables	A+, slope β-value		p-Value[#]	p-Value[$]	A−, slope β-value		p-Value[^]	p-Value[&]	p-Value*
	MDS	NO-MDS			MDS	NO-MDS			
1. Neuropsychological assessments									
ADAS	0.259	0. 177	0.002	0.21	0.038	0.031	0.930	0.270	0.004
MEM	−0.034	−0.021	0.410	0.62	−0.007	−0.206	0.200	0.430	0.039
EF	−0.156	−0.086	<0.001	0.100	−0.019	−0.034	0.520	0.160	<0.001
2. Imaging characteristics									
Hippocampus volume, mm^3	−185.4	−154.6	<0.001	0.009	−96.31	−80.59	0.310	0.460	0.004
Entorhinal volume, mm^3	−91.53	−87.88	0.008	0.360	−29.40	−29.90	0.550	0.950	0.005
Mid-temporal volume, mm^3	−448.6	−335.3	0.008	0.290	−159.1	−158. 1	0.820	0.320	<0.001
FDG-PET SUVr	−0.023	−0.018	0.310	0.690	−0.002	−0.003	0.920	0.340	0.008

#: p-value for slope difference between group A+ / MDS and A+ / NO-MDS in model-1; $: p-value for slope difference between group A+ / MDS and A+ / NO-MDS in model-2.^: p-value for slope difference between group A- / MDS and A- / NO-MDS in model-1; &: p-value for slope difference between group A- / MDS and A- / NO-MDS in model-2.*: p-value of MDS × A × VISCODE interaction in model-1.

3.2. Synergistic effects of depressive symptoms trajectory with A status on neurodegeneration and cognitive decline

A total of 584 participants (mean age = 72.6 years, education years = 16.1, female = 55.6 %) were enrolled to examine the interaction of depressive symptoms trajectory with amyloid status. Compared to amyloid-negative individuals, those who were amyloid-positive tended to have a higher proportion of MCI ($p = 0.0024$) (S-Table 1).

The likelihood ratio test indicated that the three-way interaction of CMS × A status × VISCODE accounted for a significant amount of variance in cognitive performances, including ($p = 0.049$ for memory function and $p = 0.034$ for executive function) and neurodegeneration ($p = 0.014$ for FDG-PET, p = 0.002 for hippocampus, $p = 0.0016$ for entorhinal cortex, $p = 0.0008$ for mid-temporal cortex). Similarly, significant interactions for IDS × A status were also observed for neurodegeneration and cognitive decline, including general cognition and executive function, when NDS and CMS were separately regarded as the reference group (Table 3, S-Table 4). Greater rates of decline were observed in the A+ group with IDS, compared with other groups. Individuals with IDS experienced faster neurodegeneration and cognitive decline only in the A+ group, but not in the A− group ($p < 0.001$ for general cognition, p < 0.001 for memory function, and p < 0.001 for executive function; p < 0.001 for hippocampus). The results remained unchanged in the sensitivity analyses.

3.3. Interaction of depressive symptoms intensity with A status on neurodegeneration and cognitive decline

A total of 1218 individuals (mean age = 72.6 years, education years = 16.3, female = 49.1 %) who had at least two follow-up visits were included to test whether the mean intensity of depressive symptoms could moderate the relationship of A status with neurodegeneration and cognitive decline. Among the participants, 33.4 % were amyloid-positive individuals with high-burden depressive symptoms. Compared to individuals with only amyloid-positive or with only high-burden depressive symptoms, those who were simultaneously amyloid-positive and had high-burden depressive symptoms tended to have a higher prevalence of diabetes ($p = 0.036$) (S-Table 2).

We found significant interaction effects of depressive symptoms intensity × A status in influencing brain atrophy ($p = 0.0001$ for hippocampus, $p = 0.0039$ for entorhinal cortex, p = 0.0001 for mid-temporal cortex) and executive function ($p = 0.0008$) (S-Table 5). Greater rates of cognitive decline were observed in the amyloid-positive and high depressive symptoms intensity group (A+/high-burden), compared with other groups (S-Table 5). Statistical comparison of the model coefficients indicated that high depressive symptoms intensity could predict cognitive decline in the amyloid-positive group, but not in the amyloid-negative group. Adding additional covariates didn't result in a significant change in the results.

3.4. Interaction between depressive symptoms and A status on incident AD risk

A total of 1090 non-demented participants (mean age = 72.7 years, 48.5 % female) were included for analyses, among whom 209 participants (20.1 %) developed probable AD dementia during an average of 3.9 years (max = 10 years) follow-up. Those with A+/MDS were associated with a higher risk of developing AD dementia (hazard ratio = 5.23, 95 % CI = 2.40 to 11.38, $p < 0.001$) than those with A+/NO-MDS, A−/MDS, and A−/NO-MDS (S-Fig. 1, Table 4).

Table 3
Synergistic effects of depressive symptom trajectory with A status on neurodegeneration and cognitive performance.

Variables	A+, slope β-value		p-Value[#]	p-Value[$]	A−, slope β-value		p-Value[^]	p-Value[&]	p-Value*
	NDS	IDS			NDS	IDS			
1. Neuropsychological assessment									
ADAS	0.167	0.397	<0.001	0.460	−0.022	0.006	0.910	0.510	0.0039
MEM	−0.060	−0.178	<0.001	0.550	0.015	0.020	0.470	0.870	0.691
EF	−0.082	−0.213	0.0050	0.011	0.003	−0.043	0.900	0.720	0.018
2. Imaging characteristics									
Hippocampus volume, mm^3	−162.3	−242.1	<0.001	0.310	−76.70	−66.51	0.670	0.580	0.0001
Entorhinal volume, mm^3	−89.65	−139.2	0.410	0.110	−20.82	−33.02	0.950	0.480	0.0012
Mid-temporal volume, mm^3	−452.7	−590.2	0.062	0.440	−134.7	−166. 1	0.830	0.780	0.0005
FDG-PET SUVr	−0.008	−0.020	0.190	0.320	−0.004	−0.016	0.280	0.910	0.0070

#: p-value for slope difference between group A+ / NDS and A+ / IDS in model-1; $: p-value for slope difference between group A+ / NDS and A+ / IDS in model-2.^: p-value for slope difference between group A- / NDS and A- / IDS in model-1; &: p-value for slope difference between group A- / NDS and A- / IDS in model-2.*: p-value of depressive symptoms trajectory × A × VISCODE interaction in model-1.

Table 4
Interaction between depressive symptoms and A status on incident AD risk.

Groups	Incident AD	Total sample	Model 1[&]		Model 2[&]	
			HR & 95 % CI	*p*-Value	HR & 95 % CI	*p*-Value
Baseline MDSs						
A−/NO-MDS*	209	1062	1.00	Reference	1.00	Reference
A−/MDS	209	1062	1.17 (0.50 to 2.70)	0.72	1.15 (0.50 to 2.67)	0.74
A+/NO-MDS	209	1062	3.62 (1.58 to 8.28)	0.013	3.46 (1.50 to 7.98)	0.004
A+/MDS	209	1062	5.23 (2.40 to 11.38)	<0.001	5.04 (2.30–11.02)	<0.001
Depressive symptoms trajectory						
A−/NDS*	40	357	1.00	Reference	1.00	Reference
A−/CMS	40	357	1.18 (0.34 to 4.06)	0.79	1.37 (0.40 to 4.76)	0.61
A+/NDS	40	357	2.84 (1.11 to 7.25)	0.029	2.85 (1.11 to 7.34)	0.03
A+/CMS	40	357	3.58 (1.41 to 9.11)	0.007	3.91 (1.46 to 10.50)	0.007
A−/NDS*	40	288	1.00	Reference	1.00	Reference
A−/IDS	40	288	1.40 (0.36 to 5.51)	0.63	1.56 (0.37 to 6.60)	0.54
A+/NDS	40	288	3.25 (1.27 to 8.32)	0.01	3.34 (1.29 to 8.67)	0.01
A+/IDS	40	288	10.45 (3.86 to 28.27)	<0.001	12.79 (4.29 to 38.13)	<0.001
A−/CMS*	36	205	1.00	Reference	1.00	Reference
A−/IDS	36	205	3.28 (1.03 to 10.41)	0.044	3.59 (1.11 to 11.62)	0.033
A+/CMS	36	205	1.31 (0.29 to 5.88)	0.72	1.32 (0.29 to 6.07)	0.72
A+/IDS	36	205	7.38 (2.21 to 24.59)	0.001	8.38 (2.49 to 28.28)	0.0006
Exposure intensity^						
A−/Low-burden*	209	1048	1.00	Reference	1.00	Reference
A−/High-burden	209	1048	2.48 (0.95 to 6.44)	0.06	2.24 (0.85 to 5.86)	0.10
A+/Low-burden	209	1048	8.85 (3.27 to 23.96)	<0.001	9.27 (3.368to 25.38)	<0.001
A+/High-burden	209	1048	13.99 (5.72 to 34.19)	<0.001	12.83 (5.22 to 31.54)	<0.001

& Model 1 was adjusted for age, gender, education, apoe4 status, and clinical diagnosis at baseline.Model 2 was adjusted factors in model 1 plus hypertension, diabetes, stroke, smoking, hyperlipidemia, depression, and insomnia.* Reference group; ^ Exposure intensity = total GDS score × years with symptoms / total follow-up years.

When depressive symptoms trajectory was used as an independent variable, those with A+/IDS exhibited a higher risk of developing AD compared to A−/NDS (hazard ratio = 10.45, 95 % CI = 3.86 to 28.27, $p < 0.001$, Fig. 2B, Table 4) or A−/CMS group (hazard ratio = 7.38, 95 % CI = 2.21 to 24.59, $p = 0.001$, Fig. 2C, Table 4). Additionally, those with A+/CMS also exhibited a higher risk of developing AD compared to A−/NDS (hazard ratio = 3.58, 95 % CI = 1.41 to 9.11, $p = 0.007$, Fig. 2A, Table 4). Finally, those with A+ and a high burden of cumulative depressive symptoms exhibited a higher risk of developing AD dementia (hazard ratio = 13.99, 95 % CI = 5.72 to 34.19, $p < 0.001$, Table 4). The results remained unchanged after adding more covariates (Table 4).

4. Discussion

The present study found that 1) MDS could enhance the detrimental effects of amyloid pathology on neurodegeneration and cognitive decline in the pre-dementia stage; 2) the co-existence of MDS and amyloid pathology predicted a specifically higher risk of incident AD. These findings strengthened strong connections between mild depressive symptoms and amyloid-β in the context of AD, indicating that early recognition and management of depressive symptoms could be a promising approach to lowering AD risk at the preclinical or prodromal stages of the AD continuum.

Our findings are consistent with recent longitudinal cohort studies that amyloid pathology moderated the association between worsening depressive symptoms and declining cognition in adults (Gatchel et al., 2019). Compared to previous studies, our study adds value to the growing body of evidence supportive of a close interplay between amyloid pathology and depressive symptoms in contributing to neurodegeneration, especially AD. On the other hand, Donald R. Royall et al.

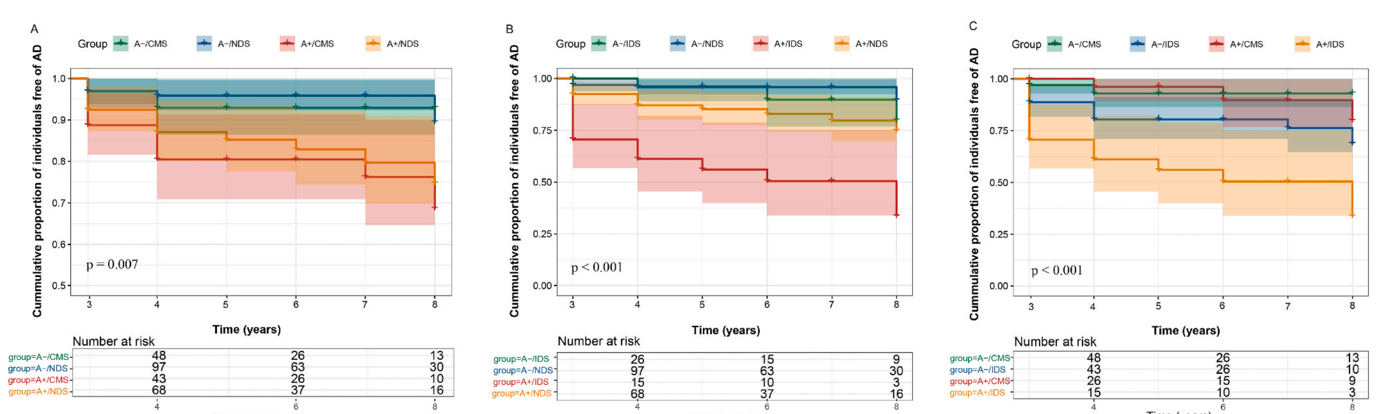

Fig. 2. Kaplan-Meier plot of the cumulative probability of AD risk.
Kaplan-Meier plot of the cumulative probability of AD risk in A−/NDS, A−/CMS, A+/NDS, A+/CMS group (A), A−/NDS, A−/IDS, A+/NDS, A+/IDS group (B), and A−/CMS, A−/IDS, A+/CMS, A+/IDS (C).
Abbreviations: NDS: no depressive symptoms; CMS: consistent minimal symptoms; IDS: increasing depressive symptoms.

(Royall and Palmer, 2013) found that neuritic plaques (NP) formed by the deposition of Aβ cannot mediate the relationship of depressive symptoms with cognitive decline. Similarly, R. Scott Mackin et al. (Mackin et al., 2021) suggested that memory deficits and accelerated cognitive decline associated with late-life depression are not attributed to increased cortical Aβ accumulation. The differences may be attributed to several factors. Firstly, our sample was not limited to individuals over the age of 65. Secondly, there is no gold standard for assessing depressive symptoms, and the measurement methods used in the studies varied. Thirdly, the interaction between MDS and amyloid-β may be influenced by other mechanisms, such as tau-mediated neurodegeneration and neuroinflammation.

Several explanations can be used to explain the interaction between depressive symptoms and amyloid in the imaging changes and cognitive decline in Alzheimer's disease (Fig. 3). Firstly, MDS could potentially contribute to the deposition of amyloid beta (Aβ), and a cross-sectional analysis has shown that the causal relationship between depressive symptoms and amyloid pathology might be bidirectional (Xu et al., 2021b; Wang et al., 2022a). Secondly, depressive symptoms have been implicated in suppressed hippocampal neurogenesis (Kreisel et al., 2014), which could result in an accelerated accumulation of toxic proteins, such as Aβ and tau protein. Thirdly, depressive symptoms might also contribute to a downstream event, such as neuroinflammation (Fee et al., 2017; Prévot and Sibille, 2021), which in turn drives amyloid deposition. Our previous study indicated that the association of MDS and amyloid pathology was partially mediated by sTREM2, a microglial marker in CSF (Wang et al., 2022b). Additionally, other possible pathways that could be involved include a dysfunctional hypothalamic-pituitary-adrenal axis (Wang et al., 2022a), an altered GABA (gamma-aminobutyric acid) system, or a disordered brain-derived neurotrophic factor, (Chi et al., 2014) all of which were shared in impaired conditions observed in both MDS and amyloidosis condition (Caraci et al., 2010). The roles of these pathways (Lutz et al., 2020) in mediating interactions of depressive symptoms with amyloid pathology warrant further investigation, as they could be potential targets for early intervention to prevent AD.

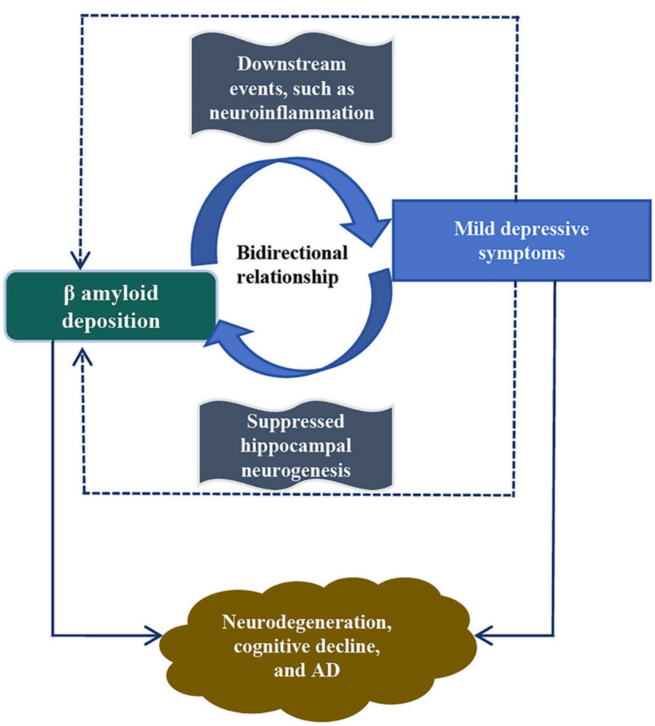

Fig. 3. Hypotheses proposed to explain the interaction effect between mild depressive symptoms and Aβ on neurodegeneration, cognitive decline, and AD risk.

Although the pathophysiological mechanism underlying this association remains unclear, the present study provided evidence linking amyloid levels, mild depressive symptoms, and neurodegeneration including AD. These findings may have important implications for future precise therapy of AD. Disease-modifying therapy (DMT) targeting amyloid pathology has been recently validated to eliminate Aβ deposits in the brain, decrease neuronal damage, and improve cognitive function (Sims et al., 2023). Future studies are warranted to test the efficacy of this amyloid-targeting DMT in populations exposed to specific exposures which are found to be interacted with amyloid pathology in AD occurrence, such as MDS. In addition, according to a recent report (Sheline et al., 2014) in cognitively normal subjects, amyloid levels are expected to decrease in subjects treated with serotonin reuptake inhibitors (SSRI). Thus, future studies are needed to examine the interaction effects of amyloid-DMT with traditional anti-depression managements in postponing AD progression, especially in populations with early depressive symptoms or major depression diagnosis.

The key strength of the present study is that depressive symptoms were defined by using baseline status, trajectory group, and mean intensity during follow-up. These approaches lead to objective capture of intraindividual variability in symptoms or the longitudinal course of depressive symptoms. Some limitations also existed to raise caution when we tried to interpret these findings. First, our study used CSF biomarkers of amyloid deposition but not PET imaging, because only a small proportion of the sample had amyloid PET data. Though a high concordance between CSF marker and PET has been reported in ADNI, misclassification bias cannot be totally excluded. Second, MDS is a concept similar to "minimal symptoms" which is only used for research but not for clinical utility. Future studies are needed to refine the cutoffs of this concept to better characterize this population. Third, the absence of comprehensive data on prior depression, including the number of episodes and age at onset, precluded its inclusion as a covariate in the current model. Future research should incorporate detailed information on depression history to more thoroughly investigate the interplay between MDS and amyloid-β. Fourth, these are preliminary findings based on an observational design which cannot equal to a causal relationship. Future experiments are thus warranted to uncover the potential pathways for mediating the interaction of depressive symptoms with amyloid pathology. Fifth, the generalizability of our findings could be constrained because ADNI participants are volunteers, more large-scale community-based longitudinal studies are warranted to validate these associations.

In conclusion, these findings highlighted an interaction between mild depressive symptoms and amyloid pathology in influencing neurodegeneration, cognitive decline, and AD risk. The co-existence of the two conditions defined a specifically high-risk population of AD. Dynamic monitoring and active management of these symptoms could potentially have a significant impact on cognitive decline and neurodegeneration, particularly in individuals with evidence of cerebral amyloid deposition.

Abbreviations

ADNI	Alzheimer's Disease Neuroimaging Initiative
AD	Alzheimer's disease
Aβ	amyloid-β
MDS	Mild Depressive symptoms
MCI	Mild cognitive impairment
NC	normal cognition
GDS	Geriatric Depression Scale
BIC	Bayesian information criteria
NDS	no depressive symptoms
CMS	consistent minimal depressive symptoms
IDS	increasing depressive symptoms
CSF	cerebrospinal fluid

ADAS	Alzheimer's Disease Assessment Scale
EF	executive function
MEM	memory function
MMSE	Mini-Mental State Examination
FDG	Fluorodeoxyglucose
A+	amyloid-positive
A−	amyloid-negative
NP	neuritic plaques
GABA	gamma-aminobutyric acid
DMT	Disease-modifying therapies
FDA	Food and Drug Administration
SSRI	serotonin reuptake inhibitors

Ethics approval and consent to participate

The ADNI was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives according to the 1975 Declaration of Helsinki.

Consent for publication

Not applicable.

Funding

This study was supported by the Taishan Scholar Project (NO. tsqn202211375).

CRediT authorship contribution statement

Xiao-Hui Zhang: Writing – original draft, Visualization, Formal analysis. **Chen-Chen Tan:** Writing – review & editing, Visualization, Formal analysis. **Ya-Wen Zheng:** Writing – review & editing. **Xiao Ma:** Writing – review & editing. **Jun-Nan Gong:** Writing – review & editing. **Lan Tan:** Writing – review & editing. **Wei Xu:** Writing – review & editing, Supervision, Software, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

All data are available upon reasonable request or can be obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

Acknowledgements

The authors thank contributors, including the staff at Alzheimer's Disease Centers who collected samples used in this study, patients, and their families whose help and participation made this work possible. Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: 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 & Development, LLC.; Johnson & Johnson Pharmaceutical Research & 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 is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (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 at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.08.235.

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