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Associations of Anxiety with Amyloid, Tau, and Neurodegeneration in Older Adults without Dementia: A Longitudinal Study

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Abstract.
Background: The pathophysiological process of amyloid-β, tau deposition, and neurodegeneration of Alzheimer's disease (AD) begin in a preclinical phase, while anxiety is associated with an increased risk of AD in preclinical phase.
Objective: To examine the relationships between anxiety and amyloid-β, tau deposition, and neurodegeneration. To test the hypothesis that anxiety could predict clinical progression in the elderly without dementia.
Methods: 1,400 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were included in the study and were studied over a median period of 3 years. In multivariable models, the cross-sectional and longitudinal associations between anxiety and amyloid-β PET, tau PET, and FDG PET SUVRs in participants without dementia were explored using Spearman rank correlation, logistic regression model, multiple linear regression model, Kaplan-Meier survival curves, and Cox proportional hazards model. The association between baseline anxiety and clinical progression was also explored.
Results: There was a positive correlation between anxiety and amyloid-β deposition ($r = 0.11$, $p = 0.0017$) and a negative correlation between anxiety and neurodegeneration ($r = -0.13$, $p = 0.00022$). MCI participants with anxiety showed a faster clinical progression of dementia (HR = 1.56, $p = 0.04$). Non-anxious participants with more amyloid-β deposition or more severe neurodegeneration displayed accelerated development into anxiety (HR = 2.352, $p < 0.0001$; HR = 2.254, $p < 0.0001$).
Conclusion: Anxiety was associated with amyloid-β deposition and neurodegeneration in non-dementia elderly. Anxiety in MCI predicted conversion to dementia. Anxiety may play a selective role and prediction of disease progression in the early phase of AD.

Keywords: Alzheimer's disease, amyloid-β, anxiety, biomarkers, dementia, neurodegeneration, tauopathies

[1]The longitudinal data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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.

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INTRODUCTION

The pathophysiological process of amyloid-β, tau deposition, and neurodegeneration of Alzheimer's disease (AD) begin in a preclinical phase which can be many years before the onset of clinical symptoms [1–3]. Neuropsychiatric symptoms are of interest to clinicians and researchers who focus on dementia because apart from impairment of memory, neuropsychiatric symptoms also play an important role in preclinical AD [4, 5]. Anxiety, which is among these neuropsychiatric symptoms has been revealed to be associated with an increased risk of AD [6, 7], suggesting that anxiety might be a target for AD prevention.

There is emerging evidence that anxiety is associated with AD biomarkers both during the preclinical period and the clinical period of AD. It has been found that higher amyloid-β burden was associated with increased anxious-depressive symptoms over time in cognitively normal old people [3] and subcortical neurofibrillary tangle accumulation was found to be associated with anxiety in dementia patients [8]. Anxiety has also been revealed to be related to AD cerebrospinal fluid (CSF) markers in mild cognitive impairment (MCI) patients by some studies: the presence of anxiety was associated with abnormal CSF t-tau concentration in MCI patients [9]. However, another study found that there was only a weak association between anxiety and elevated cortical amyloid-β deposition among cognitively normal elderly persons [10]. Also, and some studies found no association between mild behavioral impairment (which includes anxiety) and tau or neurodegeneration in cognitively intact elderly individuals [11]. These ambiguous consequences of studies, lack of study investigating the association between anxiety and AD biomarkers in cognitively normal people and lack of longitudinal studies have inspired us to further investigate the correlation between anxiety and AD biomarkers. More comprehensive understandings of the associations among anxiety, amyloid-β, tau deposition, and neurodegeneration act importantly in prognosing among older adults without dementia.

Herein, to further elucidate the relationships between anxiety and amyloid-β, tau deposition, and neurodegeneration in subjects with normal cognition and MCI, we aimed to explore 1) the correlations between anxiety and amyloid-β, tau deposition, and neurodegeneration by cross-sectional analyses; and 2) the longitudinal associations between anxiety and amyloid-β, tau deposition, and neurodegeneration. We expected anxiety as an early sign of the underlying neuropathologic changes before the onset of clinical symptoms of dementia. Additionally, we hypothesized baseline anxiety symptom would predict clinical progression in individuals without dementia.

MATERIALS AND METHODS

Alzheimer's disease neuroimaging initiative

We obtained data (including the baseline demographic characteristics, positron emission tomography (PET) data, the Neuropsychiatric Inventory score) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. ADNI was launched by the NIA, National Institute of Biomedical Imaging and Bioengineering, private pharmaceutical companies, and nonprofit organizations in 2003 collecting information of magnetic resonance imaging (MRI), PET, biological markers, clinical and neuropsychological assessments to test whether these data can be combined to measure the progression of MCI and early AD.

The principal investigator of this initiative is Michael W. Weiner, MD, the VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a wide range of academic institution and private corporations. Subjects were recruited from over 50 sites across the USA and Canada. For up-to-date information on ADNI, visit http://www.adni-info.org. The ADNI was approved by medical ethics committees of all participating institutions. Written informed consent was obtained from all participants.

Participants

Based on the data from ADNI, we selected the data of 1,400 normal and MCI individuals available with the anxiety score of the Neuropsychiatric Inventory (NPI-a), amyloid-β PET, tau PET, and FDG PET. The longest follow-up year of the individuals in the present study was 9 years. The inclusion criteria for individuals without cognitive impairment or with MCI was described as follows: normal individuals had a Mini-Mental State Examination (MMSE) score of 24 to 30 and a Clinical Dementia Rating Sum of Boxes (CDR-SB) score of 0, and normal activities of daily living (ADL) assessed with the Functional Activity Questionnaire (FAQ), without memory complaints. MCI subjects had memory complaints and had objective memory impairment indicated by the

Wechsler Memory Scale Logical Memory II, a global CDR score of 0.5 and a score equals to or more than 0.5 on the memory box of the CDR, preserved ADL assessed by the FAQ, and absence of dementia [12, 13].

Assessment of anxiety symptom

The NPI was designed to assess the neuropsychiatric symptoms by evaluating the symptoms in both frequency and severity and NPI has established reliability and validity and was the most commonly used measure both in clinical and research settings when it comes to the assessment of neuropsychiatric symptoms [14, 15]. The NPI includes 10 fields of neuropsychiatric symptoms which are elusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior, from which we chose the score of anxiety (NPI-a). The total anxiety score is a multiplication of the frequency and severity of anxiety symptom. Frequency has a scale from 0 to 4, while severity has a scale from 1 to 3. In that case, the multiplication score, as well as the total anxiety score, has a scale from 1 to 12. In our study, the NPI-a scores of the individuals with no anxiety symptom present were recorded as score 0 and greater score indicated greater anxiety. Participants were classified into two groups according to the NPI-a score, in which 0 was defined as an absence of anxiety symptom and 1–12 were defined as a presence of anxiety on the basis of prior studies [16–22]. Participants were classified into NPI-a positive (NPI-a+, $n = 134$) and NPI-a negative (NPI-a -, $n = 1266$) groups by their baseline NPI-a score.

PET acquisition and processing

PET analysis data were obtained from UC Berkeley and Lawrence Berkeley National Laboratory. Amyloid-β PET imaging was measured with florbetapir and tau PET was measured with floTaucipir. A native-space MRI scan for each subject that is segmented and parcellated with Freesurfer (version 5.3.0) was used to define cortical grey matter regions of interest (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) that make up a summary cortical region of interest (ROI). The cortical summary ROI was divided by the whole cerebellum reference region. A florbetapir cutoff of 1.11 using the whole cerebellum reference region was taken, which was equivalent to the upper 95% confidence interval above the mean of a group of young normal controls [23]. Participants were classified into amyloid PET positive group ($A+$, $n = 284$) and amyloid-β PET negative group (A-, $n = 356$). $A+$ was defined as a florbetapir SUVR above 1.11 and A- was defined as a florbetapir SUVR below 1.11. The tau PET (AV1451 PET) takeup included the amygdala, entorhinal cortex, fusiform, para hippocampal, and inferior temporal and middle temporal gyri. We took a cut point of 1.24 based on previous studies of the cut point of tau PET [24, 25]. $T+$ was defined as a floTaucipir SUVR above 1.24 and T- was defined as a floTaucipir SUVR below 1.24. Participants were classified into tau PET positive group ($T+$, $n = 89$) or tau PET negative group (T-, $n = 301$). FDG-PET data were acquired and reconstructed according to a standardized protocol. The cutoff value of FDG-PET was 1.21 [26]. $N+$ was defined as a FDG SUVR below 1.21 according to previous studies [23, 26]. Participants were classified into FDG PET positive group ($N+$, $n = 168$) or FDG PET negative group (N- , $n = 471$), respectively, according to their baseline FDG PET SUVRs.

Statistical analysis

Descriptive statistics of baseline clinical and demographics were summarized, and we tested demographic variables between NPI-a+ and NPI-a - groups separately in normal cognitive individuals and MCI individuals by using Chi-square tests (for categorical variables) and ANOVA (for continuous variables with normal contribution). Demographic variables were also tested between clinical converter and non-converter. Converter was defined as the individuals who had clinical progression from normal cognition to MCI or from MCI to dementia.

We set the baseline as the time of the first visit of the NPI-a score. In the cross-sectional analyses, we employed the baseline NPI-a score and available baseline PET SUVRs (amyloid-β, tau, FDG). In the longitudinal analyses of Kaplan-Meier plots, we chose the datasets with 1) at least two visits of PET records; and 2) the first visit of PET was negative according to the cutoff value, in order to explore the association between the baseline NPI-a status and the progression of A/T/N status (as measured by PET). To explore the associations between baseline NPI-anxiety score and the three kinds of PET SUVRs, several correlations and regression analyses were performed. Firstly, we performed Spearman correlation analyses and partial correlation to explore

the association between amyloid-β PET SUVRs and NPI-a score at the baseline. In the partial correlation, age, education, gender, *APOE* ε4 status were used as covariates. Similarly, the association between tau PET SUVRs and NPI-a score and the association between FDG glucose metabolism and NPI-a score were also explored by performing Spearman correlation analyses and partial correlation. Secondly, we carried out logistic regression analyses to evaluate the association between the three different kinds of PET SUVRs and anxiety status, which in the logistic linear regression model, age, gender, education years, and *APOE* ε4 status were used as covariates. In order to evaluate the association between clinical progression and anxiety symptom, we carried out logistic regression in which clinical progression of converter or non-converter was the binary dependent variable and NPI-a score at baseline was the independent variable. Age, gender, education years, and *APOE* ε4 status were used as covariates.

Then, we explored the longitudinal change of PET SUVRs by dividing the individuals into two groups with the criteria of baseline NPI-a score positive or not. The longitudinal change of NPI-a score was similarly explored to see whether different groups of baseline PET SUVRs positive and negative individuals had distinct trends of NPI-a score change. In addition, to access 1) the risk of progression from MCI to dementia; 2) the risk of anxiety status progression; 3) the risk of PET SUVRs change, we constructed Kaplan-Meier plots and ran multivariate Cox proportional hazards model. All statistical analyses were performed using the R statistical software (version 3.6.3). The significance level was set 0.05 for all tests.

RESULTS

Descriptive statistics

A total of 1,400 ADNI participants were included in the study, including 699 with normal cognition, 701 with MCI. In the cohort, the mean (standard deviation, SD) age was 72.2 (6.86) and among them 704 (49.6%) were women; mean (SD) years of education was 16.4 (2.58) years; 477 of them were apolipoprotein E (*APOE)* ε4 allele carriers.

Group characteristics and comparisons are presented in Table 1. In individuals with MCI, there were no significant differences between groups for age ($p = 0.395$), gender ($p = 0.76$), tau PET SUVRs ($p = 0.466$), MMSE ($p = 0.123$), and MoCA score ($p = 0.515$). NPI-a+individuals were more likely to have higher amyloid-β PET SUVRs ($p = 0.0207$) as well as have less education ($p < 0.01$). NPI-a+ individuals were more likely to be *APOE* ε4+ ($p = 0.01277$).

Converter who experienced clinical progression in the follow-up years tended to be older (Table 2, $p < 0.001$) and were more likely to be *APOE* ε4+ ($p < 0.001$). Additionally, their baseline amyloid deposition and glucose metabolism detected by PET were both significantly higher than non-converters ($p < 0.001$), as well as tau deposition ($p = 0.016$). The anxiety score was significantly higher in the converters ($p = 0.021$). The mean NPI-a score of the converters was 0.442. The MMSE score and MoCA score were significantly higher in the non-convertors ($p < 0.001$, $p < 0.001$). The mean MMSE score of the converters was 27.7 and the MoCA score of the converters was 22.7.

Table 1
Baseline demographic characteristics of the sample

	CN ($n = 699$)			MCI ($n = 701$)		
	NPI-a– ($n = 669$)	NPI-a+ ($n = 30$)	*p*	NPI-a– ($n = 597$)	NPI-a+ ($n = 104$)	*p*
Gender, female (%)	387 (57.8%)	18 (60.0%)	0.96	254 (42.5%)	42 (40.4%)	0.76
Education (SD), y	16.6 (2.47)	16.5 (2.36)	0.757	16.3 (2.59)	15.5 (3.01)	< 0.01*
Age (SD), y	72.2 (6.30)	72.1 (5.66)	0.916	72.2 (7.29)	71.6 (8.04)	0.395
APOE ε4 carriers			0.29			0.01277*
1 (%)	172 (25.7%)	7 (23.3%)		192 (32.2%)	33 (31.7%)	
2 (%)	15 (2.2%)	2 (6.7%)		40 (6.7%)	15 (14.4%)	
Aβ PET SUVRs (SD)	1.12 (0.172)	1.11 (0.189)	0.861	1.21 (0.236)	1.29 (0.215)	0.0207*
Tau PET SUVRs (SD)	1.16 (0.123)	1.22 (0.249)	0.161	1.26 (0.275)	1.32 (0.276)	0.466
FDG PET (SD)	1.31 (0.110)	1.29 (0.158)	0.293	1.25 (0.132)	1.22 (0.106)	0.0652
MMSE score (SD)	29.1 (1.17)	29.0 (1.38)	0.621	28.0 (1.81)	27.7 (2.25)	0.123
MoCA score (SD)	25.9 (2.52)	25.9 (2.95)	0.925	23.3 (3.22)	23.1 (3.05)	0.515

Data are mean (SD) or number (%) unless otherwise stated. SD, standard deviation; FDG, ^{18}F-fluorodeoxyglucose; MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; NPI-a, the score of anxiety in Neuropsychiatric Inventory; NPI-a+, NPI-a positive group; NPI-a–, NPI-a negative group; CN, cognitive normal individuals; MCI, mild cognitive impairment individuals.

Table 2
Baseline characteristic of converter and non-converter

	non-converter ($n=815$)	Converter ($n=233$)	p
Gender, female (%)	404 (49.6%)	100 (42.9%)	0.086
Education (SD), y	16.4 (2.61)	16.1 (2.73)	0.054
Age (SD), y	72.0 (6.73)	74.4 (6.89)	<0.001*
APOE ε4 genotype carriers (%)	273 (33.5%)	129 (55.4%)	<0.001*
Aβ PET SUVRs (SD)	1.13 (0.188)	1.32 (0.231)	<0.001*
Tau PET SUVRs (SD)	1.20 (0.211)	1.72 (0.494)	0.016*
FDG PET (SD)	1.30 (0.119)	1.20 (0.125)	<0.001*
NPI-a score	0.213 (0.887)	0.442 (1.39)	0.021*
MMSE score (SD)	28.7 (1.56)	27.7 (1.90)	<0.001*
MoCA score (SD)	25.0 (2.94)	22.7 (3.10)	<0.001*

Data are mean (SD) or number (%) unless otherwise stated. SD, standard deviation; FDG, 18F-fluorodeoxyglucose; MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; NPI-a, the score of anxiety in Neuropsychiatric Inventory.

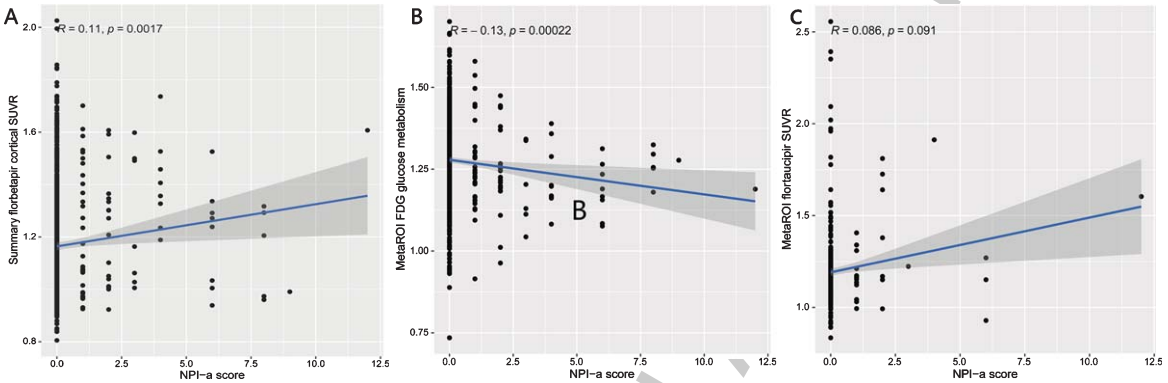

Fig. 1. Cross-sectional association between Aβ PET SUVRs, FDG PET values, tau PET SUVRs, and NPI-a score at baseline. NPI-a had a positive relationship with AV45 PET SUVRs. NPI-a had a negative relationship with FDG PET values. There was no significant relationship between NPI-a and tau PET SUVRs. NPI-a score, anxiety score from Neuropsychiatric Inventory (NPI).

Anxiety associated with more amyloid deposition and lower glucose metabolism in non-dementia

In the cross-sectional analyses, results from the Spearman correlation between the amyloid-β PET SUVRs and NPI-a score showed a positive linear relationship ($r=0.11$, $p=0.0017$; Fig. 1A). As for the result between the FDG glucose metabolism and NPI-a score, it showed a negative linear relationship ($r=-0.13$, $p=0.00022$; Fig. 1B). Partial correlation also showed a significant association between anxiety with FDG glucose metabolism ($r=-0.093$, $p=0.012$). In the logistic regression models, FDG PET showed an association with anxiety status, adjusted by age, gender, education, and *APOE* ε4 carrier (Table 3, $p=0.007$). In the longitudinal analyses, baseline amyloid-β PET positive individuals had an increased risk of conversion from anxiety negative to anxiety positive situation (Fig. 2A, $p<0.0001$). Baseline FDG PET positive individuals had an increased risk of conversion from anxiety negative to anxiety positive situation (Fig. 2B, $p<0.0001$). The cox proportional hazard model revealed that after correction for baseline age, gender, education, and *APOE* ε4, baseline amyloid-β PET positive state or baseline FDG PET positive state was still associated with a more rapid change of anxiety score (Table 5, $p<0.0001$). We did not find any significant association between anxiety and tau PET in the analyses. The results from the Spearman correlation between tau PET SUVRs and NPI-a score did not demonstrate a significant correlation ($r=0.086$, $p=0.091$; Fig. 1C). Partial correlation did not show a significant association between amyloid-β PET SUVRs and NPI-a score ($r=0.03$, $p=0.41$). Also, it did not show a significant association between tau PET SUVRs and NPI-a score ($r=0.008$, $p=0.88$). In the logistic regression models, there was no association between tau PET and anxiety status, adjusted by age, gender, education, and *APOE* ε4 carrier (Table 3, $p=0.418$).

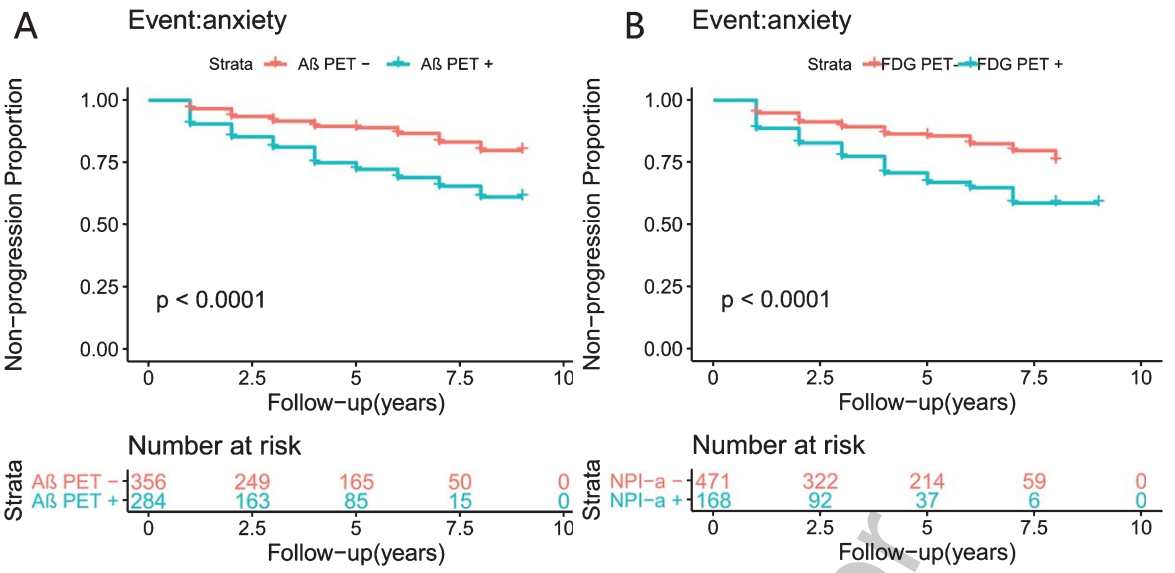

Fig. 2. Kaplan-Meier survival curves estimates for the anxiety status. Probability of non-progression from NPI- to NPI+, for different PET groups is shown. Estimated number of remaining individuals at risk of conversion to NPI+at each time point are also represented. Follow-up years' investigation revealed that individuals with baseline Aβ PET+ situation had an increased risk of conversion from anxiety negative to anxiety positive situation than individuals with baseline Aβ PET – situation. Individuals with baseline tau PET+ situation had an increased risk of conversion from anxiety negative to anxiety positive situation than individuals with baseline tau PET - situation. Aβ PET+, amyloid-β PET positive status; Aβ PET–, amyloid-β PET negative status; FDG PET+, FDG PET positive status; FDG PET-, FDG PET negative status.

Table 3
Estimates for Aβ-PET, Tau-PET, or FDG-PET for predicting anxiety status in logistic regression models

	Predictor	OR (95% CI)	*p*
anxiety status	Aβ PET SUVRs	3.12 (0.93, 10.08)	0.061
	Age	0.97 (0.93, 1.01)	0.095
	Gender (male)	1.45 (0.88, 2.41)	0.143
	Education	0.93 (0.85, 1.02)	0.132
	APOE ε4	1.60 (1.10, 2.33)	0.014*
anxiety status	Tau PET SUVRs	2.97 (0.12, 30.11)	0.418
	Age	1.01 (0.92, 1.10)	0.832
	Gender (male)	0.97 (0.30, 2.98)	0.964
	Education	0.93 (0.74, 1.19)	0.562
	APOE ε4	0.95 (0.34, 2.33)	0.923
anxiety status	FDG PET SUVRs	0.07 (0.01, 0.46)	0.007*
	Age	1.01 (0.97, 1.04)	0.719
	Gender (male)	0.81 (0.49, 1.34)	0.423
	Education	0.88 (0.80, 0.97)	0.007*
	APOE ε4	1.12 (0.75, 1.63)	0.569

Adjusted by age, gender, education, and *APOE* ε4 carrier.

Table 4
Estimates for NPI-a score for predicting converter or non-converter in logistic regression models

	OR (95% CI)	*p*
NPI-a score	1.21 (1.06, 1.38)	0.003*
Education	0.96 (0.90, 1.01)	0.092
Age	1.07 (1.04, 1.09)	< 0.001*
Gender (male)	1.19 (0.87, 1.64)	0.178
APOE ε4 carrier	2.75 (2.02, 3.76)	< 0.001*

These results indicate that the AD-related pathological changes (Aβ deposition and glucose metabolism) may interact with the development of anxiety.

NPI-a for predicting clinical progression from MCI to dementia

Logistic regression model revealed that NPI-a score, adjusted by the covariates of age, gender, education, and *APOE* ε4, was associated with clinical progression (Table 4, $p = 0.003$). Figure 3 exhibits the results of Kaplan-Meier analyses. MCI individuals with baseline NPI-a+ state had an increased risk of conversion to dementia (Fig. 3, $p = 0.037$). The cox proportional hazard model revealed that MCI participants with anxiety symptom showed a relatively faster clinical progression of dementia (HR = 1.56, $p = 0.04$). However, after correction for baseline age, gender, education, and *APOE* ε4, we did not find a significant difference between two groups (Table 6, HR = 1.48, $p = 0.059$). These results indicated that anxiety symptom evaluated by NPI-a score may help predict clinical progression in dementia. According to the adjusted cox proportional hazard model, it is possible that anxiety symptom may interact with other factors when contributing to the progression in dementia.

Table 5
Risk of progressive anxiety symptom in Aβ PET+ and FDG PET+, compared with individuals with Aβ PET– and FDG PET– as the reference

Biomarkers	Crude		Adjusted	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Aβ PET–	Reference		Reference	
AV45 PET+	2.498 (1.697,3.677)	<0.0001*	2.352 (1.528,3.620)	<0.0001*
FDG PET–	Reference		Reference	
FDG PET+	2.334 (1.597,3.411)	<0.0001*	2.254 (1.519,3.343)	<0.0001*

Adjusted by age, gender, education, and *APOE* ε4. AV45 PET+ individuals had significant risk of developing into anxiety situation compared with AV45 PET– individuals. FDG PET+individuals had significant risk of developing into anxiety situation compared with FDG PET – individuals.

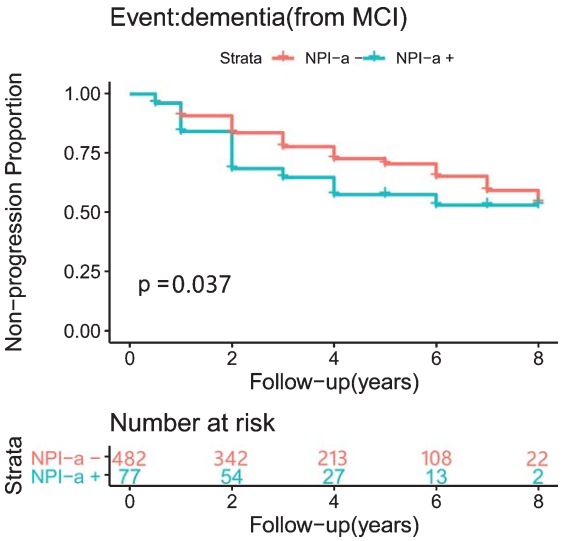

Fig. 3. Kaplan-Meier survival curves estimates for the clinical progression. Probability of non-progression from MCI to dementia, for different baseline NPI groups is shown. Estimated number of remaining MCI individuals at risk of conversion to dementia at each time point are also represented. MCI individuals with baseline NPI-a positive state had an increased risk of conversion to dementia. NPI-a–, NPI-a negative group; NPI-a+, NPI-a positive group.

Table 6
Risk of progressive cognitive deterioration (from MCI to dementia) in NPI-a+individuals compared with NPI-a - individuals as the reference

Biomarkers	Crude		Adjusted	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
NPI-a–	Reference		Reference	
NPI-a+	1.56 (1.04,2.35)	0.04*	1.48 (0.98,2.25)	0.059

Adjusted by age, gender, education and *APOE* ε4. NPI-a+ individuals had significant risk of progressive cognitive deterioration into dementia compared with NPI-a – individuals.

AD-related pathologies are not influenced by early-stage anxiety symptom

We explored whether anxiety might contribute to amyloid-β deposition, tau deposition, and glucose metabolism in MCI. In both of the linear regression models and logistic regression models, adjusted by age, gender, education, and *APOE* ε4 carrier, no statistical significance was found for NPI-a score predicting amyloid-β PET, tau PET, and FDG PET (Supplementary Tables 1 and 2). Similarly, we did not observe an increased risk of conversion from PET negative to PET positive state for individuals with baseline NPI-a+ situation (Supplementary Figure 1). These results suggested that anxiety symptom at the early stage of AD may not contribute to the AD related pathology.

DISCUSSION

We performed an exploratory study of the associations between anxiety and amyloid-β deposition, tau deposition, neurodegeneration in the elderly without dementia. 1400 participants were included. However, due to the lack of follow-up diagnostic information of 352 participants, 1048 participants were analyzed in the longitudinal study of clinical progression. With regard to the amyloid-β biomarker, we found that the presence of anxiety symptom at baseline is associated with higher baseline amyloid-β deposition. Also, we found that individuals with amyloid-β PET positive situation at the baseline show a faster increase of NPI-a score during the follow-up years, and the same group of people were more possible to change from anxiety negative to anxiety positive situation. These suggest a link between anxiety and amyloid-β deposition in AD. The Cox progression adjusted for baseline age, gender, education and *APOE* ε4 helped to reveal that amyloid-β PET positive individuals

were more likely to develop into anxiety situation than individuals who did not carry such amyloid-β burden did. Our study is consistent with recent studies which focused on the association between anxiety and amyloid-β deposition. Harvard Brain Study (HABS) recruited 270 community-dwelling, cognitively normal elderly individuals and collected their baseline Pittsburgh compound B (PiB) PET to measure their cortical aggregate amyloid-β and collected their annual assessments with the 30-item Geriatric Depression Scale (GDS). They found that higher amyloid-β burden was associated with increasing anxious-depressive symptoms over time in cognitively normal older individuals [3]. Similarly, Mayo Clinic Study of Aging (MCSA) enrolled in 1,627 participants who were non-demented and ≥ 50 years of age and conveyed NPS (neuropsychiatric inventory questionnaire) assessment and amyloid-β PET neuroimaging. The study revealed that MCI with amyloid-β burden of the brain was associated with an increased risk of having NPS as compared to MCI without amyloid-β burden [27]. As for the possible mechanism, it might be that the association between anxiety and amyloid-β deposition is mediated by cognitive status. In other words, cognitive status might act as a mediator on the relationship between amyloid-β and anxiety [28].

Investigation of the association between NPI-a score and the tau biomarker category did not lead to a discovery that baseline NPI-a score was associated with more baseline tau deposition. Follow-up years' investigation did not provide any evidence of the hypothesis that individuals with baseline NPI-a positive situation had a faster increase of tau PET SUVRs. According to previous studies, mixed findings were reported for the association between anxiety and tau biomarker. Our result is consistent with some previous research. One study indicated that levels of CSF p-tau were not associated with severity of anxiety and phobias in AD dementia [29]. However, a study which used the data from two large cohort studies, the Dutch Prisoner Institute – ADNI, showed that higher levels of CSF levels of p-tau were associated with the presence of anxiety [30]. Further association is needed to investigate the association between anxiety and tau marker.

With regard to the neurodegeneration biomarker category, we showed that cross-sectional analyses indicated the association between baseline NPI-a score and FDG PET uptake. The observed result is in accordance with a research of a cross-sectional study of cognitively normal persons aged > 70 years conducted by Mayo Clinic Study of Aging showing a significant association between abnormal FDG-PET and anxiety symptoms [31]. Longitudinal analyses gave us an evidence that individuals with lower FDG glucose metabolism level at baseline were more possible to change from anxiety negative position to the anxiety positive position. The Cox progression adjusted for baseline age, gender, education, and *APOE* ε4 revealed the longitudinal relationship between anxiety and FDG glucose metabolism. Our research was consistent with a research which used the data from two large cohort studies, the Dutch Parelsnoer Institute – ADNI, and showed that higher levels of cerebrospinal fluid levels of t-tau were associated with the presence of anxiety [30] (CSF t-tau is regarded as a biomarker of neurodegeneration in AD continuum [32]).

These findings depicted the close relationships of anxiety with amyloid-β deposition and neurodegeneration. These results also indicated that anxiety symptom evaluated by NPI-a score may help predict clinical progression in AD.

There were certain strengths in our study. Firstly, the data was recruited from a relatively long follow-up cohort collected from ADNI database and focused on both cross-sectional and longitudinal analyses based on reliable data. Secondly, our study elucidated the association of symptom of anxiety and all of the three of AD biomarkers, extending prior work by providing the evidence of what important role anxiety might play in AD neuropathological changes from a more comprehensive perspective. Thirdly, the individuals in the study were people without cognitive impairment, which provided valuable evidence and possible suggestions for diagnosing and interfering with AD patients in a relatively early stage, especially meaningful considering the heavy burden and irreversible course of AD after clinical onset.

There are limitations in this study. To begin with, although the whole cohort is a relatively large one, the data of NPI-a score is still too limited to separate the participants into two different groups (cognitively normal individuals and MCI individuals). As a result, it was not possible for us to explore the role anxiety played in the cognitively normal individuals who might be in an earlier stage of AD. Another limitation to our study was the lack of longitudinal data for tau PET and NPI-a score; in other words, there are not enough data of individuals with both tau PET and NPI-a score data in the follow-up years, which made the exploration of the association between anxiety and tau deposition not comprehensive. Further

investigation should incorporate longitudinal data in order to determine the association between anxiety and tau.

CONCLUSIONS

Our finding suggested that non-dementia population with anxiety may have higher amyloid-β deposition and more severe neurodegeneration. MCI patients with anxiety symptom have a higher risk of developing dementia. Cognitively unimpaired elderly population with higher amyloid-β deposition and more severe neurodegeneration may have a higher risk of developing anxiety. To sum up, our study supports that amyloid-β deposition and neurodegeneration may interact with anxiety symptoms in non-dementia elderly. Among MCI individuals, diagnosis of anxiety may help provide a possible indication of progression from MCI to dementia. Also, early detection of AD pathology and approaches taken may help slow down the anxiety symptom from aggravating.

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SUPPLEMENTARY MATERIAL

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