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The Relationship Between Anxiety and Incident Agitation in Alzheimer's Disease

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Abstract.
Background: Agitation in Alzheimer's disease (AD) has been hypothesized to be an expression of anxiety, but whether anxiety early in the course of dementia could be a risk factor for developing later agitation is unknown.
Objective: We used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the longitudinal relationship between anxiety and incident agitation in individuals with a diagnosis of AD at baseline or during follow-up.
Methods: Longitudinal neuropsychiatric symptom data from AD individuals who were agitation-free at study baseline ($N = 272$) were analyzed using mixed effects regression models to test the longitudinal relationship between baseline and incident anxiety with incident agitation.
Results: Anxiety at baseline was not associated with subsequent agitation, but there was a positive linear relationship between incident anxiety and agitation over the study duration. Baseline apathy and delusions were consistently associated with subsequent agitation and greater disease severity and illness duration also appeared to be risk factors for agitation.
Conclusion: Our findings support the concept that anxiety and agitation are likely to be distinct rather than equivalent constructs in mild-moderate AD. Future longitudinal cohort studies are needed to replicate these findings and further characterize potential risk factors for agitation, such as apathy and delusions.

Keywords: Agitation, Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative, anxiety, apathy, delusions

INTRODUCTION

Agitation is a distressing and difficult-to-treat neuropsychiatric syndrome, seen commonly in dementia. A consensus definition of agitation characterized the syndrome as sustained, observed, or inferred evidence of emotional distress associated with excessive motor activity or verbal or physical aggression [1]. In Alzheimer's disease (AD), agitation affects around 30% of community [2] and 80% of care home resident individuals [3]. Agitation significantly reduces quality of life and precipitates earlier institutionalization [4], but in terms of treatment, the best evidence is for short-term use of antipsychotic drugs, which have only modest efficacy and potential harmful side-effects. As agitation in dementia may have many different etiologies [5], including AD-related brain changes [6, 7], there is a clear need to better understand what may influence individuals' risk of developing agitation in order to develop better targeted prevention and treatment strategies.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://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 analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Neuropsychiatric symptoms (NPS) in AD have been related to the neuropathological processes of the disease [8] and emerge in phases from preclinical (e.g., anxiety, depression) [9] to symptomatic AD (e.g., agitation, delusions, hallucinations). It has been hypothesized that agitation (an observed behavior) in AD individuals could be an expression of anxiety (a subjective feeling) [10, 11], implying that the former could replace the latter as dementia progresses and that anxiety early in the course of dementia could increase the risk of later developing agitation. Consistent with this hypothesis, anxiety typically emerges in the preclinical stages of AD [8, 9] and has a lower prevalence in those with severe AD [12, 13], whereas agitation increases in prevalence with disease progression and worsening severity of cognitive impairment [14–16]. However, anxiety does not fully encompass all the behavioral aspects of agitation, and the overlap between them is unclear [12]. An understanding of whether AD individuals who experience early NPS, such as anxiety, have an increased risk of developing later agitation would aid clinical decision-making and stimulate further research, including the potential impact of early anxiety treatment to prevent emergence of agitation later in the disease course.

To our knowledge, only one study [17] has investigated the relationship between anxiety and agitation in AD. The study, which was cross-sectional and involved 40 participants, found a positive correlation between anxiety and agitation. The current study used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the longitudinal relationship between anxiety and incident agitation in individuals with a diagnosis of AD at baseline or during follow-up. We tested the hypothesis that agitation in AD could be an expression of anxiety and predicted that: 1) AD individuals with baseline anxiety would be more likely to develop subsequent agitation than those without baseline anxiety, and 2) the emergence of anxiety and agitation in individual participants over the study period would be negatively correlated (i.e., inversely related), as anxiety tended to be replaced by agitation as AD severity worsened.

METHODS

Subjects

All data used in the preparation of this article were obtained from the ADNI database (https://adni.loni.usc.edu). ADNI was launched in 2003, with the primary goal of testing whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological dementia markers, and structured clinical and neuropsychological assessment can be combined to measure the progression of patients with mild cognitive impairment (MCI) and AD. ADNI enrolls participants from 57 sites in the United States and Canada between the ages of 55 and 90 years who have a diagnosis of mild AD, MCI, or are normal controls. Written informed consent was obtained from all participants and recruitment was approved by the Institutional Review Boards of all of the participating institutions. Full details of ethics approval, study design, participant recruitment, and clinical testing have been published previously and are available at https://adni-info.org.

NPI-Q

The Neuropsychiatric Inventory Questionnaire (NPI-Q) is a brief version of the Neuropsychiatric Inventory (NPI) and provides a validated, informant-based assessment of the presence and severity of neuropsychiatric symptoms and associated caregiver distress [18]. The NPI-Q differs from the NPI by being a 2-page self-administered questionnaire, completed by informants about the patients for whom they care, as opposed to an interview. Each of the 12 symptom domains is assessed by a written screening question derived from the NPI. Initial responses to each screening question are "Yes" (present) or "No" (absent). If the symptom is present, the informant rates the symptom severity within the last month using a 3-point scale (mild, moderate or severe) and any associated caregiver distress with a 5-point scale (from not distressing at all to extremely distressing).

For the purposes of this study, an individual with AD was defined as having anxiety or agitation if the Anxiety or Agitation/Aggression NPI-Q subscales at a follow-up visit were marked as present. Descriptions of the NPI-Q Anxiety and Agitation/Aggression subscales are included in Table 1.

The study included all individuals from the ADNI database (Phases 1, GO, 2 and 3), diagnosed with AD at any follow-up visit and who had NPI-Q data. To analyze incident agitation over the study period, we defined the first incidence of agitation as occurring when a person who had been agitation-free at baseline subsequently developed agitation during follow-up. We therefore excluded participants with baseline agitation from the original study population to obtain the 'at risk' sample for analyses.

Table 1
Description of the NPI-Q Anxiety, Agitation/Aggression, and three additional subscales that contributed to the composite agitation measure (Disinhibition, Irritability/lability, and Motor disturbance)

NPI-Q subscale	Description
Anxiety	Does the patient become upset when separated from you? Does he/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?
Agitation/Aggression	Is the patient resistive to help from others at times, or hard to handle?
Disinhibition	Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?
Irritability/lability	Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?
Motor disturbance	Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

Statistical analyses

The baseline characteristics of the 'at risk' study population ($N = 272$) and the frequencies of anxiety and agitation over the study period were described using means and standard deviations or frequencies and proportions, as appropriate. These were compared to the baseline characteristics of the excluded sample ($N = 97$) using Welch's *t*-test for group means and Pearson's chi-squared test for proportions.

We used two mixed effects logistic regression models within the 'at risk' subsample ($N = 272$), to examine the longitudinal relationship between anxiety and incident agitation in individuals with AD over the study period. Mixed effects models can account for the correlation between repeated measures due to unobserved inter-individual heterogeneity by incorporating random effects. They can also account for unequal follow up intervals by including time as a continuous variable, and for missing data by using maximum likelihood estimation, which uses all available data. We used a 'prospective' model to investigate the relationship between baseline anxiety and incident agitation, and an alternate 'concurrent' model to examine the relationship between incident anxiety and agitation at the same follow-up timepoints, without an implied sequential relationship.

Three sets of regressions were conducted for each model: 1) unadjusted, 2) adjusted for baseline and incident NPI-rated measures (delusions, hallucinations, depression, elation/euphoria, apathy, disinhibition, irritability and motor disturbance) for the 'prospective' and 'concurrent' models respectively, and 3) adjusted for sociodemographic factors (baseline age in years, years of education, MMSE score at each timepoint, and sex).

As agitation prevalence has been shown to increase with worsening disease severity [14–16], we explored whether the relationship between anxiety and agitation in the two models was influenced by disease progression and severity, via interaction terms between anxiety and time (in months), and baseline diagnostic group (either AD or MCI/CN), respectively. To test whether our findings were sensitive to a broader, subscale definition of agitation, composed of NPI-Q rated agitation/aggression, irritability, disinhibition, and/or aberrant motor behavior [19, 20], we repeated the analyses with agitation defined as a composite within which at least three of these items were present. These NPI-rated measures were not included as covariates in the adjusted models that used the composite agitation measure. Descriptions of the NPI-Q Irritability/lability, Disinhibition, and Motor disturbance subscales are shown in Table 1.

Cross-sectional analyses were performed in R version 3.5.1 and mixed effects regression analyses were performed using STATA/MP 16.0. The relationships between variables were tested at a significance level of $\alpha = 0.05$. We used random intercept models and tested the fit of adding random slopes to the model using the likelihood ratio test (LRT). The LRT was also used to assess model fit after the addition of the interaction terms, adjustment for NPI-Q and sociodemographic variables as described above.

RESULTS

Participant characteristics

A total of 369 individuals from the ADNI database had a diagnosis of AD and were assessed using the NPI-Q. The 'at risk' ($N = 272$) population was obtained after excluding 97 individuals who had NPI-rated agitation at baseline (see Table 2 for baseline characteristics of this population). Within the 'at risk' sample (agitation-free at baseline), 47% (127 out of 272) subsequently developed NPI-Q rated agitation

Table 2
Baseline characteristics of the 'at risk' study population ($N = 272$) and excluded sample ($N = 97$)

Baseline characteristics	'At risk' sample $N = 272$	Excluded sample $N = 97$
	N (%) or mean [SD]	
Sex*		
Female (%)	120 (44)	58 (60)
Male (%)	152 (56)	39 (40)
Age in years (mean [SD])	75.4 [7.4]	74.1 [6.7]
Education in years (mean [SD])	15.3 [3.1]	14.9 [3.1]
MMSE (mean [SD])	24.9 [2.6]	25.1 [2.5]
Rate of cognitive decline (MMSE/year) (mean [SD])	–2.4 [3.1] for AD –1.7 [1.7] for CN/MCI	–2.3 [3.4] for AD –2.2 [2.5] for CN/MCI
Diagnosis		
AD (%)	138 (51)	48 (49)
CN/MCI (%)	134 (49)	49 (51)
Anxiety*		
Present (%)	60 (22)	44 (45)
Absent (%)	212 (78)	53 (55)
Developed agitation (NPI-Q)		
Yes (%)	127 (47)	–
No (%)	145 (53)	–
Developed agitation (composite)		
Yes (%)	112 (41)	–
No (%)	160 (59)	–

The two populations differed in terms of sex and baseline anxiety, indicated by (*). The composite subscale of agitation was defined as present if individuals had at least three of NPI-rated agitation, disinhibition, irritability, and aberrant motor behavior rated as present.

Table 3
Frequencies of anxiety and agitation in the 'at risk' study population ($N = 272$) at baseline

Follow-up time (months)	Total N	Anxiety		Agitation (NPI-Q)		Agitation (composite)	
		N	%	N	%	N	%
0 (baseline)	272	60	**22**	0	**0**	3	**1**
6	261	65	**25**	60	**23**	22	**8**
12	245	81	**33**	55	**22**	26	**11**
18	123	30	**24**	26	**21**	10	**8**
24	210	82	**39**	46	**22**	21	**10**
30	6	1	**16**	2	**33**	0	**0**
36	97	29	**30**	18	**19**	7	**7**
42	4	1	**25**	2	**50**	1	**25**
48	25	9	**36**	7	**28**	1	**4**
54	3	1	**33**	0	**0**	0	**0**

The composite subscale of agitation was defined as present if individuals had at least three of NPI-rated agitation, disinhibition, irritability, and aberrant motor behavior rated as present.

over the study period of up to 54 months. Around half of these participants had a baseline diagnosis of AD ($N = 138$) and the other half had progressed to AD from a baseline diagnosis of MCI or healthy control (CN) ($N = 134$). The excluded baseline agitation sample had a higher proportion of participants who were female ($\chi^2(1) = 7.0, p = 0.008$) and had baseline anxiety ($\chi^2(1) = 19.2, p < 0.001$), compared to the 'at risk' sample. The frequency of anxiety and agitation at each timepoint in the 'at risk' sample is summarized in Table 3.

Relationship between baseline anxiety and incident agitation

The prospective model showed no relationship between baseline anxiety and incident agitation within individuals over the study period (see Table 4). Similar results were obtained using either the NPI-Q rated or composite subscale definition of agitation, and before and after adjustment for other NPI-Q items and demographic factors. Baseline apathy, delusions, and a longer duration of disease were consistently

Table 4
'Prospective' model to assess the longitudinal relationship between baseline anxiety and incident agitation within 'at risk' individuals

	Model variables	Baseline anxiety	Time (months)	Group (AD versus MCI/CN)	Baseline NPI-A (delusions)	Baseline NPI-B (hallucinations)	Baseline NPI-D (depression/ dysphoria)	Baseline NPI-F (elation/ euphoria)	Baseline NPI-G (apathy/ indifference)	Baseline NPI-H (disinhibition)	Baseline NPI-I (irritability/ lability)	Baseline NPI-J (motor disturbance)
Agitation/aggression (NPI-Q)	*OR*	1.2	**1.1**	**2.2**	–	–	–	–	–	–	–	–
	(95% CI)	(0.6–2.3)	**(1.0–1.1)****	**(1.2–3.9)****								
	AOR-1	0.9	**1.1**	**1.8**	**3.7**	0.9	1.1	2.9	**2.2**	0.8	**2.2**	0.6
	(95% CI)	(0.5–1.7)	**(1.0–1.1)****	**(1.0–3.2)****	**(1.0–13.6)****	(0.0–23.2)	(0.6–2.1)	(0.6–14.8)	**(1.1–4.4)****	(0.2–2.4)	**(1.2–4.2)****	(0.2–1.7)
	AOR-2	0.8	**1.0**	1.6	**3.7**	1.0	1.0	2.7	**2.2**	0.7	**2.6**	0.5
	(95% CI)	(0.4–1.7)	**(1.0–1.10)****	(0.9–3.0)	**(1.0–13.9)****	(0.0–27.4)	(0.5–1.9)	(0.5–14.7)	**(1.1–4.5)****	(0.2–2.3)	**(1.3–4.9)****	(0.2–1.5)
Agitation (composite)	*OR*	1.4	**1.1**	**3.8**	–	–	–	–	–	–	–	–
	(95% CI)	(0.5–3.7)	**(1.0–1.1)****	**(1.6–9.1)****								
	AOR	0.8	**1.1**	**2.6**	**6.4**	1.1	1.8	**7.0**	**2.8**	–	–	–
	(95% CI)	(0.3–2.3)	**(1.0–1.1)****	**(1.1–6.0)****	**(1.3–32.4)****	(0.0–59.1)	(0.8–4.4)	**(1.3–38.6)****	**(1.1–7.2)****			
	AOR-2	0.8	**1.0**	1.9	**6.5**	1.1	2.1	4.8	**2.9**	–	–	–
	(95% CI)	(0.3–2.3)	**(1.0–1.1)****	(0.7–4.7)	**(1.2–33.9)****	(0.0–61.8)	(0.8–5.2)	(0.8–28.0)	**(1.1–7.8)****			

Values are odds ratios (to 1 decimal place) for baseline agitation measured in the 'at risk' sample ($N = 272$) using multivariate random effects models, with 95% confidence intervals (CI) before (OR) and after adjustment for other baseline NPI-rated covariates (AOR-1) and demographic factors (baseline age, MMSE at each timepoint, sex, years of education; AOR-2). The variables that had interaction terms with anxiety worsened the fit of the unadjusted model according to the LRT so were not included in this or subsequent models. Statistically significant results ($p < 0.05$) are highlighted in bold and indicated by (**), otherwise results were not significant. The composite subscale of agitation was defined as having at least three of NPI-rated agitation, disinhibition, irritability, and aberrant motor behavior being present.

associated with incident agitation in all regressions. Of those symptoms included in the agitation composite (motor disturbance, disinhibition, irritability), only baseline irritability was significantly associated with NPI-Q-rated agitation over the study period. Baseline diagnosis of AD (versus MCI/CN) was related to incident agitation but this did not survive adjustment for demographic factors (AOR-2 model), which accounted for MMSE scores.

Relationship between incident anxiety and agitation

Longitudinal analysis using the concurrent model showed that the presence of incident anxiety and agitation were significantly related at each follow up visit over the study period, before and after adjustment for other NPI-Q and demographic variables (Table 5). A longer duration of follow-up (in months) and a baseline diagnosis of AD versus MCI/CN were associated with incident agitation, but this was not consistently found in all regressions. Depression and apathy were consistently associated with agitation in all regressions, and delusions were related to the composite, but not single, NPI-Q measure of agitation. The other constituent symptoms of the composite agitation subscale (disinhibition, irritability/lability and motor disturbance) were individually related to NPI-Q-rated agitation over the study period.

For all models, the inclusion of baseline diagnosis and duration of follow-up as interaction terms with anxiety worsened the fit of the unadjusted model and were thus removed from subsequent models. Longitudinal analyses were performed using random intercept models as the addition of random slopes did not improve model fit. The addition of other NPI-Q rated variables to the unadjusted model (AOR-1) improved the model fit. Lower MMSE scores were significantly associated with incident agitation (composite NPI) in the prospective model and a longer duration of education was related to incident agitation (single NPI) in the prospective model.

DISCUSSION

This study analyzed a longitudinal cohort ($N = 272$) of patients with AD who were agitation-free at baseline, to investigate whether the presence of baseline or incident anxiety was related to the development of agitation, over the study period. Contrary to our hypothesis, we found that baseline anxiety was not associated with subsequent agitation, whereas there

Table 5
'Concurrent' model to assess the longitudinal relationship between incident anxiety and agitation at the same follow-up time points within 'at risk' individuals

	Model variables	Incident anxiety	Time (months)	Group (AD versus MCI/CN)	Incident NPI-A (delusions)	Incident NPI-B (hallucinations)	Incident NPI-D (depression/ dysphoria)	Incident NPI-F (elation/ euphoria)	Incident NPI-G (apathy/ indifference)	Incident NPI-H (disinhibition)	Incident NPI-I (irritability/ lability)	Incident NPI-J (motor disturbance)
Agitation/aggression (NPI-Q)	*OR*	**2.7**	**1.1**	**1.9**	–	–	–	–	–	–	–	–
	(95% CI)	**(1.8–4.2)****	**(1.0–1.1)****	**(1.1–3.3)****								
	AOR-1	**1.6**	**1.0**	1.5	1.1	0.7	**1.6**	0.5	**1.8**	**3.9**	**3.3**	**2.0**
	(95% CI)	**(1.0–2.5)****	**(1.0–1.1)****	(0.9–2.5)	(0.6–2.3)	(0.3–2.0)	**(1.1–2.5)****	(0.2–1.3)	**(1.2–2.8)****	**(2.3–6.6)****	**(2.1–5.0)****	**(1.1–3.5)****
	AOR-2	**1.6**	**1.0**	1.4	1.1	0.7	**1.6**	0.5	**1.8**	**3.9**	**3.4**	**2.0**
	(95% CI)	**(1.0–2.4)****	**(1.0–1.1)****	(0.8–2.4)	(0.5–2.1)	(0.2–2.0)	**(1.0–2.4)****	(0.2–1.3)	**(1.2–2.8)****	**(2.3–6.6)****	**(2.2–5.3)****	**(1.1–3.5)****
Agitation (composite)	*OR*	**6.2**	**1.0**	**3.0**	–	–	–	–	–	–	–	–
	(95% CI)	**(3.1–12.2)****	**(1.0–1.1)****	**(1.3–7.0)****								
	AOR	**4.0**	1.0	**2.4**	**2.5**	1.0	**2.1**	2.7	**3.3**	–	–	–
	(95% CI)	**(2.0–7.9)****	(1.0–1.1)	**(1.1–5.4)****	**(1.1–6.1)****	(0.3–3.6)	**(1.1–3.9)****	(0.8–9.2)	**(1.7–6.2)****			
	AOR-2	**3.8**	1.0	1.9	**2.5**	0.7	**2.3**	2.5	**3.0**	–	–	–
	(95% CI)	**(2.0–7.6)****	(1.0–1.1)	(0.8–4.7)	**(1.0–6.2)****	(0.2–2.9)	**(1.2–4.4)****	(0.7–8.9)	**(1.6–5.8)****			

Values are odds ratios (to 1 decimal place) for baseline agitation measured in the 'at risk' sample ($N = 272$) using multivariate random effects models, with 95% confidence intervals (CI) before (OR) and after adjustment for other incident NPI-rated covariates (AOR-1) and demographic factors (baseline age, MMSE at each timepoint, sex, years of education; AOR-2). The variables that had interaction terms with anxiety worsened the fit of the unadjusted model according to the LRT so were not included in this or subsequent models. Statistically significant results ($p < 0.05$) are highlighted in bold and indicated by (**), otherwise results were not significant. The composite subscale of agitation was defined as having at least three of NPI-rated agitation, disinhibition, irritability, and aberrant motor behavior being present.

was a positive linear relationship between incident anxiety and agitation over the study period. These results were sensitive to the single NPI-Q measure and a broader composite definition of agitation. Our findings do not support the concept that agitation is an expression of, or replaces, anxiety as AD progresses, nor that early anxiety is a risk factor for later development of agitation in mild-moderate AD. Instead, the results are consistent with the idea that anxiety and agitation are distinct rather than equivalent constructs, as reported in previous studies [12, 17], which considered them to be separate clinical entities rather than part of a broader syndrome.

In line with prior studies [14–16], AD progression (duration of follow-up) and severity (a baseline diagnosis of AD versus MCI/CN) appeared to be risk factors for agitation in our sample. An original observation from this study is that baseline apathy and delusions were associated with subsequent agitation. The NPI-Q Apathy/Indifference subscale asks "Does the patient seem less interested in his/her usual activities or in the activities and plans of others", and the Delusion subscale asks "Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way".

The ability to detect and integrate emotional and sensory stimuli underlies complex behaviors such as salience assignment and goal-directed behaviors, and requires intact fronto-subcortical networks [21, 22]. Apathy is common in AD and its frequency and severity are correlated with the severity of cognitive impairment [23]. Evidence suggests that, rather than being at opposite ends of a behavioral spectrum, agitation and apathy share common neuroanatomical features involving overlapping structures (frontal, anterior cingulate, orbitofrontal cortices, amygdala, and insula) [7, 24–26] and may co-present within a "dysexecutive syndrome" [27, 28]. Agitation in AD has been associated with dysfunction in multiple neurotransmitter networks, especially the noradrenergic and serotonergic systems [6], and the same neurotransmitter systems have been implicated in apathy in other neurodegenerative disorders such as frontotemporal lobar degeneration [29] and Parkinson's disease [30, 31]. There is also evidence that dysregulated dopamine signaling in the mesocorticolimbic network contributes to both apathy (via impaired motivation) [32], and delusion formation (via abnormal salience attribution to sensory stimuli) [33, 34]. Interestingly, baseline irritability was associated with subsequent NPI-rated agitation, and both irritability and agitation have been proposed to result

from heightened threat perception and impaired emotion regulation [7, 35]. Future studies in longitudinal AD cohorts are needed to investigate whether baseline apathy, delusions (and irritability) may be early clinical manifestations of neurobiological changes underlying subsequent agitation in AD.

Limitations

The 'at risk' sample consisted of individuals who were agitation-free at baseline, but we cannot exclude the possibility that this included participants who experienced agitation prior to their baseline assessment and thus were not truly 'agitation free', which may have influenced the findings. Indeed, single episodes or a relapsing course of neuropsychiatric symptoms are common in AD [36], although aggressive behavior may be more likely to follow a stable course [37]. It is also possible that baseline irritability, which was associated with NPI-rated incident agitation, represented subthreshold agitation. The exclusion of 97 patients with baseline agitation also meant that our 'at risk' sample was vulnerable to selection bias. For example, the excluded sample had a higher proportion of females, and may also have represented a subgroup who were more vulnerable to developing agitation. Our sample was a longitudinal cohort of individuals with mild-moderate AD who were followed up for up to four and a half years, but there was a significant drop-out rate from 24 months (Table 3). Although we obtained comparable results when we repeated the analyses using data up to 24 months (Supplementary file), our findings may have been affected by further selection bias. An even longer duration of follow-up (e.g., a retrospective cohort with additional data on mid-life anxiety disorders, or anxiety and agitation in severe AD) could potentially be more informative and may have exposed different trajectories of anxiety and agitation. Relatedly, earlier signs of anxiety in patients with a diagnosis of AD (versus MCI) at baseline may have been missed. As we did not have data on concurrent prescription medications or physical health markers, we were unable to account for the possible effect of drugs or physical illness (e.g., infection, pain) on agitation or anxiety symptoms throughout the study. The NPI-Q definitions of anxiety and agitation do not cover all aspects of these symptoms and may not have been as sensitive or specific as more detailed measures, such as the Rating Anxiety in Dementia (RAID) [38] or Agitated Behaviors in Dementia (ABID) [39] scales. For example, the NPI-Q definition of agitation was 'resistive behavior' and may not have captured the complexity of the agitation construct. Additionally, as an informant-based assessment, the NPI-Q was unable to directly measure patients' subjective anxiety. On the other hand, this is often challenging to assess in dementia, as in many cases the patient is unable to communicate effectively due to cognitive impairment, and the exclusive reliance on caregiver report may be the only option [12]. The study investigated the presence or absence of symptoms and did not include symptom severity or caregiver distress in the models. Although mixed effects models can account for missing data, there is still a possibility that we were unable to reject the null hypothesis due to inadequate power.

In conclusion, this retrospective longitudinal cohort study did not find evidence to support the hypothesis that early anxiety is associated with later agitation in individuals with mild-moderate AD. Disease severity and illness duration appeared to be risk factors for developing agitation. Longitudinal studies with preclinical mid-life depression, anxiety and premorbid personality measures, along with longer follow up may better characterize potential risk factors for agitation.

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SUPPLEMENTARY MATERIAL

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