


FEATURED ARTICLE

A longitudinal investigation of A β , anxiety, depression, and mild cognitive impairment

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Abstract

Introduction: We investigated the longitudinal relationship between cortical amyloid deposition, anxiety, and depression and the risk of incident mild cognitive impairment (MCI).

Methods: We followed 1440 community-dwelling, cognitively unimpaired individuals aged ≥ 50 years for a median of 5.5 years. Clinical anxiety and depression were assessed using Beck Anxiety and Depression Inventories (BAI, BDI-II). Cortical amyloid beta (A β) was measured by Pittsburgh compound B positron emission tomography (PiB-PET) and elevated deposition (PiB+) was defined as standardized uptake value ratio ≥ 1.48 . We calculated Cox proportional hazards models with age as the time scale, adjusted for sex, education, and medical comorbidity.

Results: Cortical A β deposition (PiB+) independent of anxiety (BAI ≥ 10) or depression (BDI-II ≥ 13) increased the risk of MCI. There was a significant additive interaction between PiB+ and anxiety (joint effect hazard ratio 6.77; 95% confidence interval 3.58–12.79; $P = .031$) that is, being PiB+ and having anxiety further amplified the risk of MCI.

Discussion: Anxiety modified the association between PiB+ and incident MCI.

KEYWORDS

amyloid imaging, anxiety, depression, mild cognitive impairment, Pittsburgh compound B positron emission tomography

1 | BACKGROUND

Amyloid beta (A β) deposition may precede clinical symptoms of Alzheimer's disease (AD) by about 15 to 20 years.^{1,2} The field of AD and brain aging has made substantial advances in biomarker measurements such that in living persons, cortical A β deposition can be visualized by amyloid brain imaging using various types of tracers.³

Elevated A β deposition has been associated with faster cognitive decline in cognitively unimpaired (CU) elderly^{4–7} and in persons with mild cognitive impairment (MCI).^{8,9} About 30% of CU and 60% of individuals with MCI are amyloid positron emission tomography (PET) positive.¹ The use of biomarkers is in line with the updated National Institute on Aging–Alzheimer's Association (NIA-AA) Research Framework, which recommends a biological definition of AD.

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This includes the “AD continuum,” which can be determined by amyloid imaging.¹⁰

Anxiety and depressive symptoms have also been associated with cognitive decline.^{11–14} Additionally, there is a growing body of research on the association between anxiety, depressive symptoms, and brain amyloid deposition in brain aging and cognitive decline. For example, in cross-sectional studies, we have previously observed a weak association between cortical amyloid positivity and anxiety as well as depressive symptoms in CU persons.¹⁵ Furthermore, we showed that the coexistence of MCI with elevated brain amyloid deposition was associated with higher odds of having anxiety and depression.¹⁶ Investigators from the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) observed that elevated anxiety symptoms moderated the effect of amyloid deposition on cognitive decline in a longitudinal study.¹⁷ However, large-scale longitudinal investigations of the association between A β deposition, anxiety, depressive symptoms, and MCI are lacking.

While elevated cortical amyloid deposition is an established biomarker risk for MCI,^{7,18} the key point of our analysis was to examine the relationships between anxiety and depression to MCI risk when amyloid values were available.

Therefore, we conducted a population-based study to examine the interaction between amyloid deposition and anxiety or depression in predicting the risk of MCI. We hypothesized that anxiety and depression would modify the association between cortical amyloid deposition and incident MCI in community-dwelling individuals.

2 | METHODS

2.1 | Setting

The study was conducted in the setting of the population-based Mayo Clinic Study of Aging (MCSA). We included 1440 CU participants aged ≥ 50 years who underwent baseline neuropsychological testing, Beck Depression Inventory-II (BDI-II)¹⁹ and Beck Anxiety Inventory (BAI)²⁰ assessment, as well as amyloid PET neuroimaging after the baseline evaluation. Details of the MCSA procedures have been reported elsewhere.²¹ Briefly, the MCSA is an ongoing population-based study examining the prevalence, incidence, and risk factors for MCI and dementia in Olmsted County, Minnesota. Initially the study was established in October 2004 when Olmsted County residents, aged 70 to 89 years, were enumerated and an age- and sex-stratified random sample was invited to participate in the MCSA using the Rochester Epidemiology Project (REP) resources.²² As of 2012, recruitment of residents aged 50 to 69 years began, and recruitment is continuing using the same protocols.

The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards, and informed consent for participation was obtained from every participant.

HIGHLIGHTS

- We prospectively studied 1440 community-dwelling, non-demented older persons.
- Anxiety modified the association between elevated cortical amyloid beta and incident mild cognitive impairment.
- Clinicians should consider anxiety in adults with preclinical Alzheimer's disease.

RESEARCH IN CONTEXT

1. Systematic review: Only a few longitudinal studies have examined the association between brain amyloid deposition and anxiety or depression with the outcome of cognitive decline. For example, elevated anxiety symptoms have been shown to moderate the effect of amyloid deposition on cognitive decline.
2. Interpretation: While clinical anxiety modified the association between amyloid beta and risk of mild cognitive impairment (MCI) in cognitively unimpaired (CU) individuals, depression did not. Therefore, specifically anxiety seems to impact the progression to MCI in amyloid-positive individuals.
3. Future directions: The findings show the clinical importance of anxiety in preclinical Alzheimer's disease (AD). Even though there is no effective treatment for AD, it will be crucial to identify high-risk groups at a preclinical phase to intervene once treatment is available. More research is needed to examine whether early treatment of anxiety in individuals at high risk for AD might contribute to prevention or delay of AD.

2.2 | Study design

This prospective cohort study included CU individuals on whom BDI-II, BAI, and amyloid PET data were available. Participants with a diagnosis of MCI or dementia or missing amyloid PET were excluded. CU participants with and without anxiety, depression, or elevated amyloid PET were followed forward in time for a median of 5.5 years with 95% confidence interval (CI): (5.34, 5.81). The outcome of interest was incident MCI.²³ Cognitive, anxiety, depression, and amyloid data were available on 1537 participants, of whom 92 individuals were lost to follow-up and 5 died. Therefore, the final analyses included 1440 CU participants (Figure 1).

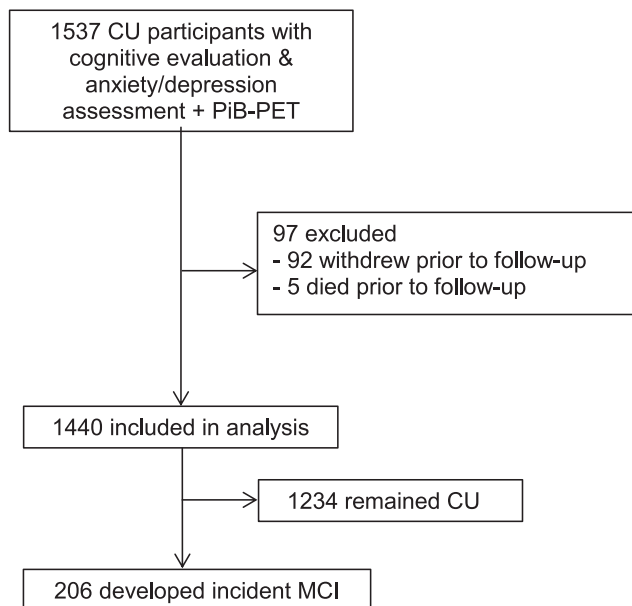


FIGURE 1 Study flowchart. CU, cognitively unimpaired; MCI, mild cognitive impairment; PiB-PET, amyloid PET imaging using the Pittsburgh compound B tracer

2.3 | Cognitive evaluation

Participants of the MCSA underwent face-to-face evaluations including risk factor ascertainment (including BDI-II and BAI) and baseline evaluation (including Clinical Dementia Rating Scale [CDR])²⁴ performed by a nurse or study coordinator; a neurologic evaluation including a neurologic interview, Short Test of Mental Status,²⁵ and neurologic examination performed by behavioral neurologists; and neuropsychological evaluation of four cognitive domains—memory (delayed recall trials from the Auditory Verbal Learning Test²⁶ and the Wechsler Memory Scale–Revised,²⁷ Logical Memory and Visual Reproduction subtests); language (Boston Naming Test²⁸ and category fluency); visuospatial (Wechsler Adult Intelligence Scale–Revised,²⁸ Picture Completion and Block Design subtests); and executive function (Trail Making Test Part B²⁹ and the Wechsler Adult Intelligence Scale–Revised,³⁰ Digit Symbol subtest). All tests were administered by psychometrists and supervised by neuropsychologists. An expert consensus panel of physicians, neuropsychologists, and nurses or study coordinators reviewed the data and determined if a participant was CU or had MCI. Classification of CU was based on normative data developed in this community.^{31–34}

The diagnosis of MCI was based on the revised Mayo Clinic criteria:²³ (1) cognitive concern expressed by a physician, informant, participant, or nurse; (2) impairment in one or more cognitive domains (executive functions, memory, language, or visuospatial skills); (3) essentially normal functional activities; and (4) absence of dementia. Participants with MCI had a CDR score of 0 or 0.5, but the final diagnosis was based on all available data.

2.4 | Measurement of anxiety and depression

Participants completed the BDI-II¹⁹ and BAI.²⁰ Both inventories are validated and consist of 21 items that measure common symptoms of depression over the past 2 weeks, and symptoms of anxiety over the last week. The severity of each symptom is rated on a Likert scale ranging from 0 to 3, with a total score ranging from 0 to 63; based on previous literature a BDI-II cutoff score of ≥ 13 indicated clinical depression,³⁵ and a BAI cutoff score of ≥ 10 indicated clinical anxiety.³⁶

2.5 | Molecular imaging–PiB-PET acquisition

We performed amyloid PET imaging using the Pittsburgh compound B (PiB) tracer. Details on PiB-PET imaging in the MCSA have been published elsewhere.^{37–38} Briefly, PiB scans, consisting of four 5-minute dynamic frames, were acquired from 40 to 60 minutes after intravenous injection with 292–728 MBq of ¹¹C-PiB. Images were analyzed using an in-house, fully automated image processing pipeline in which image voxel values were extracted from automatically labeled regions of interest propagated from regions defined on each participant's own magnetic resonance imaging (MRI). A global amyloid PET standardized uptake value ratio (SUVR) was formed from the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest and normalized to the cerebellar gray matter. Participants with an SUVR ≥ 1.48 (centiloid 22)³⁹ were classified as having an abnormal PiB-PET retention (elevated A β burden; PiB+), as beyond that cut-off rates amyloid PET reliably increased.^{37,40}

2.6 | Measurement of covariates

We defined the following variables as covariates: age, sex, education, and medical comorbidity. Comorbid medical conditions were assessed by the standard Charlson index. The Charlson Comorbidity Index predicts the 10-year mortality for a patient with a total of 22 potential comorbid conditions and was calculated using the Deyo method. Thus, a composite index was calculated after numeric values were assigned to comorbid medical conditions.⁴¹

2.7 | Statistical analysis

We conducted statistical analyses to examine the interaction between brain amyloid deposition and anxiety or depression in predicting incident MCI among CU. We calculated hazard ratios (HR) and 95% CIs using Cox proportional hazards models with age as the time scale, and adjusted for sex, education, and medical comorbidity. Clinical depression and clinical anxiety were assessed by the BDI-II (cutoff score ≥ 13) and the BAI (cutoff score ≥ 10), respectively. We used Kaplan-Meier survival curves for visual display of data, with age as a

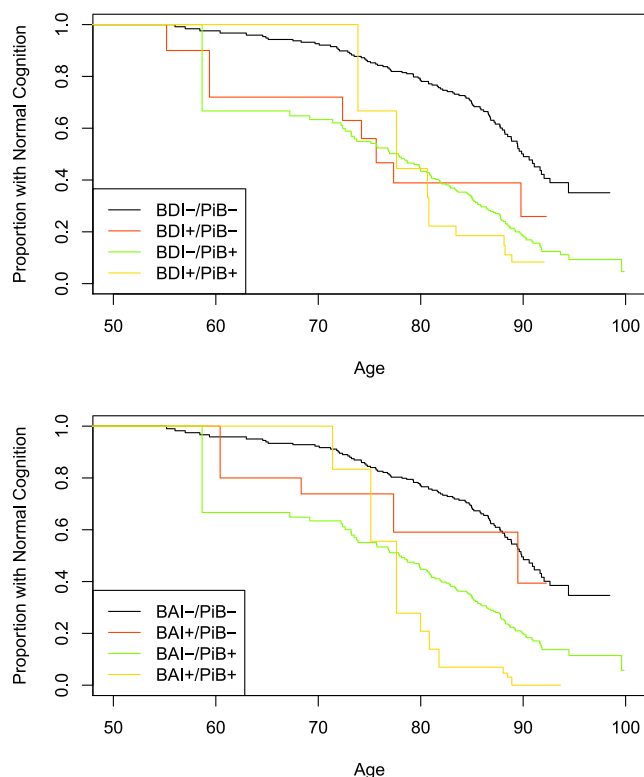


FIGURE 2 Survival curves. BDI \pm , presence/absence of depression as measured by Beck Depression Inventory-II; BAI \pm , presence/absence of anxiety as measured by Beck Anxiety Inventory; PiB \pm , participants with elevated/normal brain amyloid deposition

time scale (Figure 2). We tested for additive interaction as it is more applicable to biological events than multiplicative interaction.⁴² In our models, we compared four groups: PiB-/anxiety- (normal amyloid deposition/no anxiety; defined as reference group), PiB+/anxiety- (elevated amyloid deposition/no anxiety), PiB-/anxiety+ (normal amyloid deposition/anxiety), and PiB+/anxiety+ (elevated amyloid deposition/anxiety); equivalent to anxiety we examined similar groups using clinical depression. The proportional hazards assumption was checked for all models by looking at the Schoenfeld residuals; the assumption was met for all models. Statistical testing was performed at the conventional two-tailed alpha level of 0.05. All analyses were performed using SAS System, version 9.4 software (SAS Institute) and R version 3.6.2 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Demographics

We prospectively followed 1440 CU participants to the outcome of incident MCI or censoring for a median of 5.5 years; 1061 (73.7%) persons were PiB-PET-, 379 (26.3%) were PiB-PET+; and 206 participants (14.3%) developed incident MCI. The median (interquartile range [IQR]) age was 70.9 (63.0, 77.7) years, 52.8% were males, the median (IQR) education was 15 (13, 17) years and the median number of medi-

cal comorbidities was 2 (1, 4) as measured by the Charlson Comorbidity Index.⁴¹ The median (IQR) number of anxiety (as measured by BAI) and depressive symptoms (as measured by BDI-II) was 1 (0, 3) and 3 (1, 6), respectively; 73 (5.1%) participants showed clinical anxiety (BAI \geq 10), and 79 (5.5%) clinical depression (BDI-II \geq 13). PiB-PET+ and PiB-PET- participants differed in terms of age, education, and medical comorbidities. BDI-II data were missing for four participants. The complete demographic characteristics are summarized in Table 1.

3.2 | Associations between amyloid positivity and anxiety/depression with incident MCI

We examined whether there was an additive interaction between amyloid positivity and clinical anxiety or depression in predicting the risk of MCI. We defined the reference group as PiB- and no anxiety or depression, respectively. Compared to the reference group, PiB+ participants even in the absence of clinical anxiety (HR [95% CI]): (1.85 [1.38, 2.49], $P < .0001$) or depression (2.04, [1.52, 2.74], $P < .0001$) were at an increased risk of incident MCI. Furthermore, PiB+ participants with clinical anxiety (HR [95% CI], 6.77 [3.58, 12.79], $P < .0001$) had an increased risk of incident MCI compared to the reference group. There was a statistically significant additive interaction between amyloid positivity and clinical anxiety ($P = .0310$) in increasing the risk of incident MCI, after adjusting for sex, education, and medical comorbidity. The interaction between amyloid positivity and clinical depression in predicting the risk of MCI was not statistically significant (Table 2). Initially we adjusted for sex and education (data not shown); when we additionally adjusted for medical comorbidity the results were not altered (Table 2).

4 | DISCUSSION

Herein, we report a synergistic additive interaction between elevated cortical amyloid deposition and clinical anxiety in predicting the risk of incident MCI. Thus, the combined presence of amyloid positivity and anxiety was greater than the expected arithmetic sum of their independent effects. However, there was no significant additive interaction between amyloid positivity and depression.

Additionally, amyloid deposition increased the risk of MCI independent of depression and anxiety. Furthermore, PiB+ participants with clinical anxiety (BAI \geq 10) had an almost 7-fold increased risk of developing MCI; whereas being PiB+ without clinical anxiety was associated with almost double the risk; and having clinical anxiety and being PiB- was not statistically significantly associated with an increased risk of MCI.

We and others have reported the association between anxiety and increased risk of MCI¹³, AD, and vascular dementia.⁴³ However, these associations between clinical anxiety and risk of dementia are not necessarily etiologic associations. Therefore, studies involving biomarkers will be crucial to pave the way to understand the mechanism linking anxiety with risk of dementia.

TABLE 1 Characteristics of the study cohort at baseline

Variable	PiB-PET+ (N = 379)N (%)	PiB-PET- (N = 1061)N (%)	Total (N = 1440)N (%)	P
Males	195 (51.5)	565 (53.3)	760 (52.8)	<.5467 ^a
Age (years), median [IQR]	76.7 [70.3, 81.9]	68.0 [60.5, 75.7]	70.9 [63.0, 77.7]	<.0001 ^b
Education (years), median [IQR]	14 [12, 16]	15 [13, 17]	15 [13, 17]	.0229 ^b
Charlson index, median [IQR]	3 [1, 5]	2 [1, 3]	2 [1, 4]	<.0001 ^b
BDI-II, median [IQR]	3 [1, 7]	3 [1, 6]	3 [1, 6]	.0026 ^b
BDI-II ≥ 13 (clinical depression) ^c	21 (5.6)	58 (5.5)	79 (5.5)	.9340 ^a
BAI, median [IQR]	1 [0, 4]	1 [0, 3]	1 [0, 3]	0.6451 ^b
BAI ≥ 10 (clinical anxiety)	23 (6.1)	50 (4.7)	73 (5.1)	0.3016 ^a
PiB SUVR, median [IQR]	1.8 [1.6, 2.1]	1.4 [1.3, 1.4]	1.4 [1.3, 1.5]	< 0.0001 ^b

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; IQR, interquartile range; PiB-PET+, participants with elevated brain amyloid deposition; PiB-PET-, participants with normal brain amyloid deposition; PiB SUVR, global amyloid PET standardized uptake value ratio.

Note: P indicates difference between PiB-PET+ and PiB-PET- participants.

^ap derived from Chi square test.

^bp derived from Wilcoxon rank-sum test.

^cBDI-II information is missing on four participants.

TABLE 2 Interaction between brain amyloid deposition and anxiety/depression in predicting the risk of incident mild cognitive impairment

	No. at risk	No. of events	HR (95%CI)	P	P for additive interaction
BAI-Anxiety-/PiB-	1011	95	1.00 (ref. group)		0.0310
BAI-Anxiety+/PiB-	50	4	1.308 (0.479, 3.571)	.5999	
BAI-Anxiety-/PiB+	356	96	1.850 (1.376, 2.486)	<.0001	
BAI-Anxiety+/PiB+	23	11	6.770 (3.583, 12.791)	<.0001	
BDI-II Depression-/PiB-	1002	92	1.00 (ref. group)		0.8817
BDI-II Depression+/PiB-	58	7	1.465 (0.677, 3.171)	.3321	
BDI-II Depression-/PiB+	355	99	2.037 (1.516, 2.736)	<.0001	
BDI-II Depression+/PiB+	21	8	2.266 (1.073, 4.786)	.0320	

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; CI, confidence interval; HR, hazard ratio; PiB-PET-, participants with normal brain amyloid deposition; PiB-PET+, participants with elevated brain amyloid deposition; ref. group = reference group.

Note: Results based on Cox proportional hazards models, adjusted for age (as the time scale), sex, education, and medical comorbidity.

Whereas most studies were limited by small sample sizes and cross-sectional designs, few studies have examined the longitudinal associations between cortical amyloid deposition and the outcome of anxiety or depressive symptoms. For example, investigators from Washington University observed that amyloid deposition was associated with higher depressive symptoms as measured by Geriatric Depression Scale (GDS) after following 66 CU participants for approximately 1 year.⁴⁴ Furthermore, investigators from the community-dwelling Harvard Aging Brain Study (HABS) found that higher baseline amyloid deposition was associated with increased depressive and particularly anxious-depressive symptoms as measured by the GDS over a mean of 3.8 years in 270 CU elderly.⁴⁵

These longitudinal studies examined associations between brain amyloid deposition and the outcome of anxiety or depressive symptoms. However, to date, little is known about anxiety or depression in modifying the association between amyloid deposition and cognitive decline.

For example, HABS investigators followed 276 older persons for a mean of 4.4 years and reported a significant interaction between baseline amyloid deposition with higher depressive symptoms (as measured by GDS) on cognitive decline.⁴⁶ When we examined the association between amyloid deposition and clinical depression with the outcome of MCI, we did not find a statistically significant additive interaction between amyloid positivity and clinical depression in predicting the risk of MCI. Therefore, in our findings it seems that the addition of depression to PiB+ did not increase risk over PiB+ alone. Discrepancies in findings might be due to methodological differences (e.g., different assessment of cognitive decline and depression; also, as anxiety and depressive syndromes often overlap, confounding is possible). Thus, in the current study we examined both anxiety and depression separately and their interaction with PiB+ in increasing MCI risk.

In line with the current study, AIBL investigators conducted a longitudinal study in CU participants examining associations between amyloid deposition, depression, and anxiety with the outcome of cognitive

decline.¹⁷ They followed approximately 300 healthy, older adults (about 50% of AIBL participants had subjective memory complaints and about 50% were apolipoprotein E [APOE] ϵ 4 carriers) for 54 months and observed that increased amyloid deposition was associated with increased risk of cognitive decline compared to participants with negative amyloid imaging. In addition, elevated anxiety symptoms (as measured by the Hospital Anxiety and Depression Scale [HADS] score) moderated the effect of amyloid deposition on cognitive decline. Similar to our findings, they found no significant impact of depression in predicting or moderating the effect of amyloid deposition on cognitive decline.¹⁷

Consistent with our results, investigators from Sweden recently reported anxiety but not depression (as measured by the HADS score) to interact with amyloid status in predicting faster cognitive decline; however, they defined cognitive decline solely by Mini-Mental State Examination.⁴⁷

Our study replicates these findings and adds to the previous literature by showing a synergistic additive interaction between elevated amyloid positivity and anxiety but not depression in predicting the risk of MCI in a large population-based sample in which extensive cognitive assessment was available.

While elevated cortical amyloid deposition is an established biomarker risk for MCI,^{7,18} we examined the additional impact of anxiety and depression on MCI risk. While anxiety modified the association between $A\beta$ and risk of MCI in our cohort of CU elderly, depression did not. Therefore, specifically anxiety seems to impact the early progression from CU to MCI in amyloid-positive individuals. One possible explanation could be that anxiety occurs earlier during the preclinical phase of AD (i.e., AD continuum as defined by PiB+) even before neurodegeneration and cognitive changes occur. This is supported by previous studies that our group has conducted in the setting of the MCSA, in which anxiety was a predictor of incident MCI in CU,¹³ but it did not predict the risk of dementia in individuals with MCI.¹⁴ However, in these previous studies we did not additionally examine biomarkers like PiB, which is necessary to define the AD continuum.

Depression on the other hand has been associated with neurodegeneration⁴⁸⁻⁴⁹ and thus could play a more significant role during a later clinical stage on the AD continuum.

In the past, our team has proposed four possible theoretical explanations for the link between neuropsychiatric symptoms and dementia.⁵⁰ These theoretical constructs can also be applied for clinical anxiety. They are: (1) the etiologic pathway: anxiety may have a direct deleterious effect on the brain, for example via the hypothalamus-pituitary axis and therefore lead to dementia; in this case anxiety would be considered a "risk factor"; (2) shared risk factor or confounding pathway: $A\beta$, may be the cause of both cognitive decline and anxiety; herein anxiety could represent a "disease marker"; (3) a synergistic interaction: anxiety and $A\beta$ may have a synergistic interaction to further amplify the risk of incident dementia; and (4) reverse causality: cognitive decline may lead to reactive anxiety. Importantly, these four theoretical constructs are not mutually exclusive and remain hypothetical until empirically validated by mechanistic research.

The current study mostly supports a synergistic interaction between anxiety and $A\beta$ in increasing the risk of cognitive decline. Depression on the other hand could be part of the "shared risk factor or confounding pathway." In our results it appears that the risk of MCI in PiB+ depressed individuals is primarily driven by PiB+ and not the combination of PiB+ and depression although we need to keep in mind the sample size limitations, as well. Thus depression could be a marker of amyloid and thus preclinical AD. However anxiety seems to interact with AD pathology in increasing MCI risk. This association was beyond the effect of amyloid alone. As we do not know the exact mechanism more mechanistic research will be needed to explore this interaction further.

The strengths of our study include the large-scale, population-based cohort study and a relatively long follow-up time.

Our study also has limitations. Some of the analyzed groups had relatively low numbers, thus potentially limiting statistical power (for example, only 8 out of the 21 participants with both depression and PiB+ developed MCI, and only 11 out of the 23 participants with both anxiety and PiB+ developed MCI at follow-up). Furthermore only 4 out of the 50 participants with anxiety and PiB- developed MCI at follow-up, indicated by wider confidence intervals, which could result in inflation of the point estimates. However, low numbers in some strata are expected considering that our study sample consisted of community-dwelling persons. Furthermore, our sample is relatively highly educated and 98% of study participants are White. However, it has been shown that data from Olmsted County are generalizable to the US population of Minnesota and the Upper Midwest,⁵¹ even though generalization to ethnic minority groups is still limited.

In summary, we expand upon the previous literature by showing that clinical anxiety in community-dwelling individuals during the preclinical phase of AD increases the risk of incident MCI. Therefore, anxiety could be a very early marker of AD. Thus, assessing anxiety could be an important tool to identify patients at high risk of AD even before cognitive decline occurs. This finding has clinical implications in that the monitoring and possible management of anxiety among CU community-dwelling persons with cortical $A\beta$ deposition may be warranted. Even though there is no effective treatment for AD, it will be crucial to identify high-risk groups at an early preclinical phase to intervene once treatment is available. Furthermore, with anxiety potentially modifying the risk of cognitive decline during the preclinical phase of AD, more research is needed to examine whether early treatment of anxiety in individuals at high risk for AD might contribute to prevention or delay of AD.

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