Original Investigation

Amyloid-β, Anxiety, and Cognitive Decline in Preclinical Alzheimer Disease
A Multicenter, Prospective Cohort Study

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IMPORTANCE Alzheimer disease (AD) is now known to have a long preclinical phase in which pathophysiologic processes develop many years, even decades, before the onset of clinical symptoms. Although the presence of abnormal levels of amyloid-β (Aβ) is associated with higher rates of progression to clinically classified mild cognitive impairment or dementia, little research has evaluated potentially modifiable moderators of Aβ-related cognitive decline, such as anxiety and depressive symptoms.

OBJECTIVE To evaluate the association between Aβ status and cognitive changes, and the role of anxiety and depressive symptoms in moderating Aβ-related cognitive changes in the preclinical phase of AD.

DESIGN, SETTING, AND PARTICIPANTS In this multicenter, prospective cohort study with baseline and 18-, 36-, and 54-month follow-up assessments, we studied 333 healthy, older adults at hospital-based research clinics.

MAIN OUTCOMES AND MEASURES Carbon 11–labeled Pittsburgh Compound B (PiB)–, florbetapir F 18–, or flutemetamol F 18–derived measures of Aβ, Hospital Anxiety and Depression Scale scores, and comprehensive neuropsychological evaluation that yielded measures of global cognition, verbal memory, visual memory, attention, language, executive function, and visuospatial ability.

RESULTS A positive Aβ (Aβ+) status at baseline was associated with a significant decline in global cognition, verbal memory, language, and executive function, and elevated anxiety symptoms moderated these associations. Compared with the Aβ+, low-anxiety group, slopes of cognitive decline were significantly more pronounced in the Aβ+, high-anxiety group, with Cohen *d* values of 0.78 (95% CI, 0.33-1.23) for global cognition, 0.54 (95% CI, 0.10-0.98) for verbal memory, 0.51 (95% CI, 0.07-0.96) for language, and 0.39 (95% CI, 0.05-0.83) for executive function. These effects were independent of age, educational level, IQ, *APOE* genotype, subjective memory complaints, vascular risk factors, and depressive symptoms; furthermore, depressive symptoms and subjective memory complaints did not moderate the association between Aβ and cognitive decline.

CONCLUSIONS AND RELEVANCE These results provide additional support for the deleterious effect of elevated Aβ levels on cognitive function in preclinical AD. They further suggest that elevated anxiety symptoms moderate the effect of Aβ on cognitive decline in preclinical AD, resulting in more rapid decline in several cognitive domains. Given that there is currently no standard antiamyloid therapy and that anxiety symptoms are amenable to treatment, these findings may help inform risk stratification and management of the preclinical phase of AD.

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Alzheimer disease (AD) is now known to have a long preclinical phase in which pathophysiologic processes develop many years, even decades, before the onset of clinical symptoms.[1,2] In healthy, older adults, the presence of abnormally high levels of amyloid-β (Aβ) is associated with unremitting decline in cognitive function, particularly in verbal memory; reductions in hippocampal volume; and higher rates of progression to clinically classified mild cognitive impairment (MCI) or dementia.[3-9] However, variability in the extent to which Aβ-positive (Aβ+) status is related to cognitive decline in the preclinical phase of AD suggests that other factors may also influence Aβ+-related cognitive decline.[1,2]

Increased anxiety and depressive symptoms are related to increased Aβ in healthy, older adults and adults with MCI and AD[10,11] and are associated with reductions in memory and related aspects of cognition, such as executive function, in healthy, older adults.[12-22] However, some studies[23-25] have found that anxiety is unrelated to cognitive decline in older adults, suggesting that this effect may be explained by or that anxiety symptoms may interact with other factors with known deleterious effects on cognition, such as Aβ. Given that anxiety and depressive symptoms are amenable to prevention[26,27] and treatment,[28] even in the context of dementia,[29] their identification as potential determinants or moderators of Aβ-related cognitive decline in healthy, older adults is important for risk stratification, clinical management of individuals in the preclinical and prodromal phases of AD, and planning studies of novel antiamyloid therapies.

The aim of this study was to extend the results of a preliminary report[30] to evaluate the associations of Aβ, anxiety and depressive symptoms, and cognitive change in a large, multicenter, prospective cohort of healthy, older adults who were followed up for 4½ years. Data were analyzed from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) Study.[31] On the basis of prior work,[5-9] we hypothesized that, after adjustment for traditional risk factors for cognitive decline, such as increased age, low IQ and *APOE* ε4 genotype, Aβ+ status would be associated with greater decline in cognitive function, particularly verbal memory. We further expected that this association would be moderated by anxiety symptoms, such that Aβ+, older adults with elevated anxiety symptoms would have a greater magnitude decline in cognitive function than Aβ+, older adults with low-anxiety symptoms.

Methods

Sample

The study was approved by and complied with the regulations of the institutional research committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital, and Edith Cowan University. All participants provided written informed consent.

A total of 333 older adults who underwent Aβ neuroimaging as part of the AIBL Study[32] were included in this study. Selection into the full AIBL cohort was controlled to ensure a wide age distribution from 60 years through the very elderly (80-100 years old) and enrollment of approximately 50% of individuals with subjective memory complaints. For the 25% of this cohort who completed Aβ imaging, an additional criterion was added to enrich the sample with *APOE* ε4 carriers: enrollment of a sample composed of approximately 50% *APOE* ε4 carriers. Exclusion criteria were schizophrenia, depression (15-item Geriatric Depression Scale [GDS] score ≥6), Parkinson disease, cancer (except basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes mellitus, and current regular alcohol use (>2 standard drinks per day for women or >4 per day for men). For each assessment, a clinical review panel considered all available medical, psychiatric, and neuropsychological data to confirm the cognitive health of each participant.

PET Imaging and *APOE* Genotyping

The Aβ imaging with positron emission tomography (PET) was conducted using carbon 11-labeled Pittsburgh Compound B (PiB), florbetapir 18 F, or flutemetamol 18 F. A 30-minute acquisition was started 40 minutes after injection of PiB, whereas 20-minute acquisitions were performed 50 minutes after injection of florbetapir and 90 minutes after injection of flutemetamol. For PiB, PET standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV, yielding a region-to-cerebellar ratio termed the SUV ratio (SUVR). For florbetapir, the SUVR was generated using the whole cerebellum as the reference region; for flutemetamol, the pons was used as the reference region for the SUVR. In line with previous studies,[33-35] the SUVR was classified dichotomously as negative or positive (ie, Aβ− or Aβ+). For PiB, a SUVR threshold of 1.5 or greater was used. For florbetapir and flutemetamol, SUVR thresholds of 1.11 or greater and 0.62 or greater were used, respectively. An 80-mL blood sample was also obtained from each participant, 0.5 mL of which was sent to a clinical pathology laboratory for *APOE* genotyping.

Anxiety and Depressive Symptoms

Anxiety and depressive symptoms were assessed at the baseline visit using the Hospital Anxiety and Depression Scale (HADS).[36] Because older adults with psychiatric illness were excluded from the AIBL Study, we operationalized elevated anxiety and depression symptoms as a score greater than the median on the HADS anxiety and depression subscales for the full sample. A total score of 8 or higher on the HADS anxiety and depression subscales is indicative of clinically meaningful anxiety and depression symptoms.

Vascular Risk Factors

A count of vascular risk factors was obtained by summing[37,38] whether respondents met the criteria for hypertension (blood pressure ≥140/90 mm Hg or currently undergoing treatment with an antihypertensive medication), dyslipidemia (fasting serum total cholesterol level ≥240 mg/dL [to convert to millimoles per liter, multiply by 0.0259], fasting serum triglycerides level ≥200 mg/dL [to convert to millimoles per liter, multiply by 0.0113], or currently undergoing treatment with statin or fibrate medications), obesity (body mass index >30 [calcu-

Table 1. Demographic and Clinical Characteristics of the 333 Study Participants

Characteristic	No. (%) of Participants[a]
Age, mean (SD) [range], y	70.0 (6.8) [60-89]
Sex	
Male	160 (48.0)
Female	173 (52.0)
Educational level, y	
<9	23 (6.9)
9-12	120 (36.0)
13-15	63 (18.9)
>15	126 (37.8)
Vascular risk factors	
0	112 (33.6)
1	104 (31.2)
2	31 (9.3)
≥3	13 (3.9)
Full-scale IQ, mean (SD)	108.6 (7.1)
MAC-Q score, mean (SD)	25.3 (4.5)
HADS depression score, mean (SD)	2.6 (2.2)
HADS anxiety score, mean (SD)	4.2 (2.8)
APOE ε4 carrier	109 (32.7)
Amyloid-β positive	84 (25.2)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; MAC-Q, Memory Complaint Questionnaire.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

lated as weight in kilograms divided by height in meters squared]), smoking (ever smoked >20 cigarettes per day for more than 1 year), diabetes (fasting plasma glucose level >126 mg/dL [to convert to millimoles per liter, multiply by 0.0555] or currently undergoing treatment with diabetes medication), high homocysteine levels (males >2.19 mg/L; females >1.84 mg/L [to convert to micromoles per liter, multiply by 7.397]), or chronic kidney disease (estimated glomerular filtration rate <45 mL/min).

Subjective Memory Complaints

Subjective memory complaints were assessed using the Memory Complaint Questionnaire,[39] a 6-item scale that asks individuals to report the extent to which they experience memory difficulties in everyday situations (eg, remembering a telephone number) relative to when he or she was in high school. Scores range from 7 through 35, with scores of 25 or higher indicative of clinically significant subjective memory impairment.

Neuropsychological Assessment

Comprehensive neuropsychological evaluations were conducted at baseline and 18-, 36-, and 54-month follow-ups. Composite measures of cognitive function were derived based on theory and clinical consensus.[40] The verbal memory composite score was composed of scores on the logical memory delayed recall, delayed recall, and d' measures of the California Verbal Learning Test, Second Edition. The visual memory composite score was composed of scores on the 3-minute and 30-minute delayed recall of the Rey Complex Figure Test and the Cogstate One Card Learning Task. The executive function composite score was composed of scores on the letter fluency (FAS), category switching (fruit/furniture), and Cogstate One Back tests. The language composite score was composed of scores on the Category Fluency Test (animals' and boys' names) and the Boston Naming Test. The attention composite score was composed of scores on the Digit Span, Cogstate Detection, and Cogstate Identification tests. The visuospatial composite score was composed of scores on the copy and clock drawing tasks of the Rey Complex Figure Test. Factor analyses revealed strong loadings (ie, all factor loadings ≥0.47) of each of the component measures on these composite scores. A global cognition score was also computed by averaging scores across these cognitive domains.

Statistical Analysis

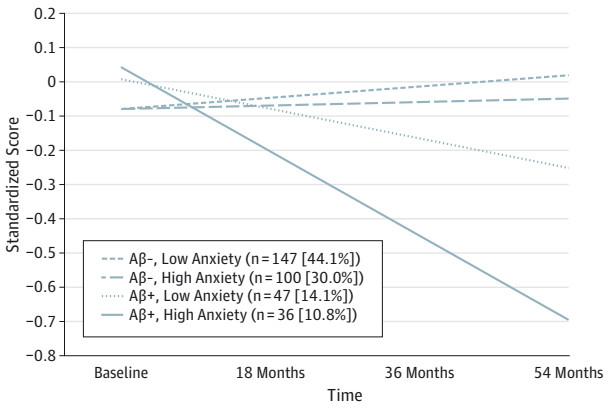
We conducted a series of linear mixed-effects models to evaluate the associations between baseline anxiety and depressive symptoms, other risk factors, and change in cognitive function during the 54-month study period. Baseline anxiety symptoms (ie, score greater than median on anxiety items of the HADS), depressive symptoms (ie, score greater than median on depression items of the HADS), amyloid level, *APOE* genotype (ε4 carrier vs non-ε4 carrier), age, sex, educational level, full-scale IQ, and Memory Complaint Questionnaire scores were entered as fixed effects or independent variables, participant as a random factor, and composite cognitive test scores as dependent variables. To evaluate the role of anxiety and depressive symptoms as moderating variables (ie, variables that influence the strength of the association between Aβ and cognitive changes), we also incorporated interaction terms (eg, Aβ × time × anxiety symptoms) into these models. If significant effects of anxiety or depressive symptoms were observed, we repeated these analyses using clinically meaningful anxiety or depressive symptoms (ie, HADS scores ≥8) to evaluate whether magnitudes of cognitive change differed as a function of severity of anxiety and depressive symptoms. Cohen *d* values and 95% CIs were computed to estimate effect sizes of group differences.

Results

Of the 333 healthy, older adults who completed a baseline assessment, 323 (97.0%), 306 (91.9%), and 296 (88.9%) completed 18-, 36-, and 54-month follow-ups, respectively. **Table 1** gives the demographic and clinical characteristics of the sample. HADS anxiety data were missing for 3 (0.9%) participants and HADS depression data were missing for 4 (1.2%) participants. Thus, the Aβ and anxiety group classification numbers and percentages shown in **Figures 1**, **2**, and **3** do not sum to 333 and 100%, respectively.

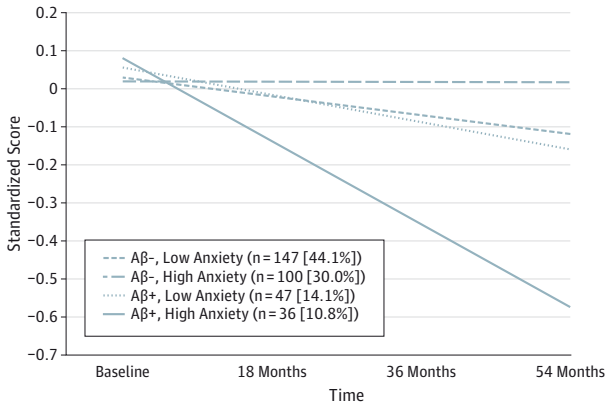
The median HADS anxiety and depression scores in the full sample were 4 and 2, respectively. The mean (SD) HADS anxiety scores in the low-anxiety (n = 194) and high-anxiety (n = 136) groups were 2.3 (1.3) and 6.9 (1.9), respectively

Figure 1. Slopes of Change in Verbal Memory Composite Score by Amyloid-β (Aβ) and Anxiety Levels



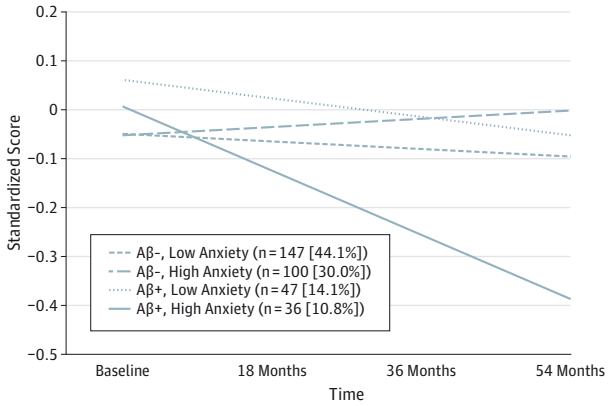
Slopes are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depressive symptoms.

Figure 2. Slopes of Change in Language Composite Score by Amyloid-β (Aβ) and Anxiety Levels



Slopes are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depressive symptoms.

Figure 3. Slopes of Change in Executive Function Composite Score by Amyloid-β (Aβ) and Anxiety Levels



Slopes are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depressive symptoms.

(t_{328} = 26.62, P < .001). The mean (SD) HADS depression scores in the low-depression (n = 202) and high-depression (n = 127) groups were 1.1 (0.7) and 4.8 (1.9), respectively (t_{327} = 24.35, P < .001). In the full sample of older adults, 45 (13.5%) and 14 (4.2%) scored 8 or higher on the anxiety and depression subscales of the HADS, respectively, which is indicative of clinically meaningful anxiety and depressive symptoms.

Table 2 gives the results of linear mixed-effects models that evaluated the association of Aβ, anxiety symptoms, and cognitive change. These analyses revealed significant effects of Aβ status on global cognition and verbal memory; anxiety symptoms on global cognition; and time on global cognition and all component aspects of cognition except visual memory. Significant interaction effects of Aβ × time on global cognition and all component aspects of cognition except attention and visuospatial function and anxiety symptoms × time on global cognition and verbal memory were also observed. Anxiety symptoms significantly moderated the association between Aβ and change in global cognition, verbal memory, executive function, and language. These effects remained significant after incorporation of Aβ × time × depressive symptoms and Aβ × time × subjective memory complaints interaction terms, which were not significant for any of the dependent variables (F < 1.99 for all, P >.054 for all).

In linear mixed-effects models with clinically meaningful anxiety symptoms entered as an independent variable, the same moderating effect of anxiety symptoms on the association between Aβ and cognitive change was observed: global cognition (F = 16.21, P < .001), verbal memory (F = 16.68, P < .001), executive function (F = 4.65, P = .03), and language (F = 4.44, P < .001). This interaction was not significant for visual memory (F = 0.05, P = .82), attention (F = 2.06, P = .15), or visuospatial (F = 0.01, P = .92) scores.

Figures 1, 2, and 3 show slopes of change as a function of baseline Aβ level and anxiety symptoms for measures of verbal memory, language, and executive function, respectively. Compared with the Aβ+, low-anxiety group, slopes of cognitive decline were significantly more pronounced in the Aβ+, high-anxiety group, with Cohen *d* values of 0.78 (95% CI, 0.33-1.23) for global cognition, 0.54 (95% CI, 0.10-0.98) for verbal memory, 0.51 (95% CI, 0.07-0.96) for language, and 0.39 (95% CI, 0.05-0.83) for executive function scores.

In analyses with clinically meaningful anxiety symptoms entered as an independent variable, slopes of cognitive decline were also more pronounced in the Aβ+, clinically meaningful anxiety group compared to the Aβ+, no clinically meaningful anxiety group, with Cohen *d* values of 1.32 (95% CI, 0.57-2.08) for global cognition, 1.41 (95% CI, 0.65-2.17) for verbal memory, 1.01 (95% CI, 0.28-1.75) for executive function, and 0.78 (95% CI, 0.06-1.50) for language scores.

Table 2. Results of Linear Mixed-Effects Models Evaluating Predictors of Cognitive Change During the 54-Month Study Period[a]

	Global Cognition		Verbal Memory		Visual Memory		Executive Function		Attention		Language		Visuospatial	
Variable	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value
Aβ positive	14.55	<.001	9.84	.002	2.67	.10	3.79	.052	2.56	.11	1.84	.17	1.17	.28
Anxiety symptoms	4.30	.04	1.52	.22	0	.99	0.02	.89	0.57	.45	0.21	.65	0	.96
Time	114.99	<.001	23.81	<.001	2.69	.10	5.86	.02	66.30	<.001	20.97	<.001	47.15	<.001
Aβ × anxiety symptoms	2.71	.10	1.15	.28	0.05	.82	0.21	.65	0.06	.80	0.70	.40	2.18	.14
Aβ × time	52.22	<.001	39.13	<.001	17.73	<.001	8.04	.005	1.08	.30	9.87	.002	2.11	.15
Anxiety symptoms × time	18.36	<.001	9.65	.002	0.55	.46	1.01	.31	0.32	.57	1.70	.19	2.59	.11
Aβ × time × anxiety symptoms	15.71	<.001	5.81	.02	1.21	.27	5.10	.02	0.02	.88	6.14	.013	0.05	.83

Abbreviation: Aβ, amyloid-β.

[a] The Aβ level reflects the mean amount of Aβ in the frontal, postcingulate, lateral temporal, and occipital cortices. Linear mixed-effects models are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depression.

Discussion

The findings of this study replicate prior work demonstrating that Aβ+ status[4,5,9-11,28] and anxiety symptoms[12,13,18] are associated with reduced memory function in healthy, older adults. These results also extend our initial report[30] to suggest that, relative to Aβ−, older adults, Aβ+, older adults have greater decline in global cognition, executive function, and language and that these associations are moderated by elevated anxiety symptoms. Specifically, among healthy, Aβ+, older adults, those with elevated anxiety symptoms had a greater decrease in these cognitive domains during a 4½-year period than Aβ+, older adults with nonelevated anxiety symptoms. The magnitudes of these effects, which were most pronounced for verbal memory, were moderate for older adults with anxiety symptoms greater than the median for the sample (d = 0.39-0.78) and large for older adults with clinically elevated anxiety symptoms (d = 0.78-1.41). Of note, moderating effects of anxiety symptoms on Aβ-related decline in these aspects of cognitive function were independent of several risk factors for cognitive decline, including advanced age, educational level, IQ, *APOE* genotype, subjective memory complaints, vascular risk factors, and depressive symptoms.

The finding that anxiety symptoms moderated the effect of Aβ-related cognitive decline is consistent with prior work demonstrating that increased levels of anxiety symptoms are related to increased Aβ in healthy, older adults, as well as in adults with MCI and AD,[10,11] and are associated with reduced memory and related cognitive functions, such as executive function.[12-18,20-22] Of note, the finding that the interaction between Aβ and time and anxiety symptoms was significant for verbal memory, language, and executive function but not any of the other cognitive functions assessed suggests that Aβ+ status and elevated anxiety have a particularly deleterious effect on aspects of cognition that are linked to temporal and prefrontal cortical functions. This finding is consistent with amyloid imaging data that suggest that Aβ accumulation is pronounced in these regions and linked to memory decline in preclinical AD.[3,41] Elevated anxiety symptoms may exacerbate Aβ-related cognitive impairment by increasing endogenous levels of glucocorticoids, which consequently damages brain regions such as the hippocampus, and result in more pronounced decline in memory and related cognitive functions over time.[12,42] Animal studies have also found that Aβ toxicity may affect hypothalamic-pituitary-adrenal axis regulation and increase levels of glucocorticoids[43] and that greater intraneuronal Aβ accumulation in the amygdala may affect amygdala-dependent emotional responses.[44] A recent study[45] in humans has further linked elevated Aβ levels to reduced modulation of entorhinal cortical activity during an episodic memory task in healthy, older adults, which may contribute to memory decline in preclinical AD. Anxiety also diverts and preoccupies prefrontally mediated attentional resources to fear- and threat-related information, which may in turn negatively affect encoding and retention of verbal information, as well as other prefrontally mediated cognitive processes, such as executive function.[12,15] The finding that anxiety symptoms, but not subjective memory complaints, were linked to cognitive decline independently and interactively with Aβ suggests that more generalized anxiety symptoms, such as worry, fearfulness, and restlessness,[36] rather than a more specific form of anxiety related to perceived memory loss, increase the risk of decline in these cognitive domains.

Taken together, these results suggest that, in healthy, older adults with elevated Aβ levels, therapeutic mitigation of elevated anxiety symptoms may help delay or slow progressive decline in verbal memory, language, and executive function. Because elevated anxiety symptoms were operationalized as symptoms greater than the median in this sample, the current results suggest that even subthreshold anxiety symptoms may exacerbate Aβ-related cognitive decline; however, the magnitudes of these moderating effects were numerically larger for clinically elevated anxiety symptoms (ie, score ≥8 on HADS anxiety subscale), suggesting that the moderating effect of anxiety symptoms on Aβ-related cognitive decline may become more pronounced as anxiety symptoms increase in severity.

Given that anxiety symptoms are amenable to treatment,[26,28,29] their identification as potential determinants or moderators of Aβ-related cognitive decline in healthy older persons may help inform risk stratification

and management of the preclinical and prodromal phases of AD before the availability of antiamyloid therapies. Anxiety symptoms have been linked to increased hippocampal activation in response to threat,[46] which suggests that treatment of anxiety symptoms may help reduce hippocampal hyperactivity and in turn help mitigate memory decline in prodromal AD. Selective serotonin reuptake inhibitors promote hippocampal neurogenesis,[47,48] and some evidence suggests that they may also help improve memory and global cognition in MCI[49] and AD.[50] A recent study[51] of healthy adults also found that, relative to placebo, a single dose of the selective serotonin reuptake inhibitor citalopram was associated with a 37% reduction in Aβ production in cerebrospinal fluid, suggesting that selective serotonin reuptake inhibitors may also directly influence Aβ levels. Further research is needed to evaluate the efficacy of pharmacotherapeutic, psychotherapeutic, and combined interventions in mitigating cognitive decline in Aβ+, older adults. One potential hypothesis to test based on the results of the current study is that, at appropriate doses, treatment with selective serotonin reuptake inhibitors or other anxiolytic medications may improve memory and related aspects of cognitive function in Aβ+ individuals at risk for AD.

Methodologic limitations of this study must be noted. First, the AIBL cohort of healthy, older adults who completed amyloid imaging was intentionally composed of equal proportions of adults with subjective memory complaints and *APOE* ε4 carriers. Thus, additional studies are required to determine the extent to which the results of this study may be generalized to population-based samples of older adults. Second, because older adults with psychiatric illness and GDS scores of 6 or higher were excluded, the presence or absence of anxiety and depressive symptoms was operationalized on the basis of a median split procedure. Thus, it remains to be determined whether a certain threshold or profile of anxiety or depressive symptoms may have a stronger moderating effect on Aβ-related cognitive decline or whether this effect is linked to any subthreshold elevation of anxiety symptoms. Therefore, excluding potential participants on the basis of GDS scores but not an anxiety measure may, at least in part, account for the lack of a significant effect of depressive symptoms in predicting and moderating the effect of Aβ on cognitive decline because a greater proportion of the sample had clinically significant anxiety symptoms. Third, anxiety and depressive symptoms were assessed using a self-report inventory instead of an interview administered by a health care professional. Additional research with more clinically diverse samples that uses structured interviews administered by health care professionals will be useful in further evaluating the direct and moderating effect of anxiety and depressive symptoms on cognitive changes in preclinical AD. Fourth, although the current study focused on Aβ, other biological factors, such as neuronal loss, gliosis, and hyperphosphorylated tau protein aggregates, may also contribute to and interact with psychological symptoms to predict cognitive decline in preclinical AD; additional research is needed to evaluate this possibility.

Conclusions

Notwithstanding these limitations, the results of this study demonstrate a strong association of Aβ+ status on decline in global cognition, verbal memory, language, and executive function. They further indicate that anxiety symptoms moderate these associations, which suggests that mitigation of anxiety symptoms, even subthreshold levels, may help slow or delay cognitive decline in otherwise healthy, Aβ+, older adults. Additional research is needed to evaluate the generalizability of these results; elucidate neurobiological mechanisms that mediate the association of Aβ, anxiety symptoms, and cognitive decline; and examine the efficacy of psychotherapeutic and/or pharmacotherapeutic interventions for anxiety in mitigating cognitive decline in Aβ+, older persons.

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Author Contributions: Drs Pietrzak and Lim had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Study supervision: Neumeister, Ames, Ellis, Lautenschlager, Maruff.

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Australian Imaging, Biomarkers, and Lifestyle Research Group: A list of the members of the Australian Imaging, Biomarkers, and Lifestyle Research Group is available at http://aibl.csiro.au/about/aibl-research-team/.

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