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Examining the Complicated Relationship Between Depressive Symptoms and Cognitive Impairment in Preclinical Alzheimer Disease.

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Abstract

Introduction: The relationships between Alzheimer's disease (AD), cognitive performance, and depression are poorly understood. It is unclear whether depressive features are a prodrome of AD. Additionally, some studies of aging exclude depressed individuals, which may inappropriately limit generalizability. The aim of the present study was to determine whether depressive symptoms affect cognitive function in the context of preclinical AD.

Methods: Cross-sectional multivariate analysis of participants in a longitudinal study of aging (n = 356) that evaluates the influence of depressive symptoms on cognitive function in cognitively normal adults.

Results: There is no relationship between the presence of depressive symptoms and cognitive function in those with either no evidence of preclinical AD or biomarker evidence of early stage preclinical AD. However, in later stages of preclinical AD, the presence of depressive symptoms demonstrated interactive effects, including in episodic memory (0.96, 95% CI: 0.31, 1.62) and global cognitive function (0.46, 95% CI: 0.028, 0.89).

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Conclusions: The presence of depressive symptoms may be a late prodrome of AD. Additionally, studies investigating cognitive function in older adults may not need to exclude participants with depressive symptomology, but may still consider depressive symptoms as a potential confounder in the context of more extensive neuronal injury.

INTRODUCTION

Late-life depression (LLD), defined as depression in those age sixty and older, and neurodegenerative disorders such as Alzheimer's disease (AD), are often associated and may share common underlying causes[1,2]. Several studies have found persistent cognitive impairments in persons with LLD in the domains of memory, executive functioning and processing speed regardless of current mood, remission status, or treatment[3–5]. Subsyndromal symptomatic depression (SSD), defined as having depressive symptoms that do not meet criteria for clinical depression, is very common in older adults[6], and it is unclear whether there is an effect of SSD on cognition.

The relationship between dementia and conditions such as LLD and SSD is poorly understood[7]. Depression has been reported to be a prodrome or risk factor[8] for AD and may affect up to 50% of individuals with symptomatic AD. Additionally, subsyndromal depressive symptoms may[9] or may not[10] confer an increased risk of future cognitive decline. Depressive symptoms may be associated with volumetric changes in AD-related areas[11] (without correlation with amyloid burden[11,12]), but they may not have any relationship with the presence of AD biomarkers in cognitively normal older adults[13] or the degree of cognitive impairment in patients diagnosed with dementia[14]. It is unclear if depression exerts a negative effect on cognitive performance in AD.

The pathophysiology underlying AD begins decades before the manifestation of clinically relevant symptoms[15], a condition referred to as "preclinical AD". *In vivo* biomarkers, including concentrations of cerebrospinal fluid (CSF) β-amyloid$_{1–42}$ (A$\beta_{1–42}$), total tau (t-tau), phosphorylated tau (ptau$_{181}$), and neuroimaging indicators of β-amyloid binding such as [^{11}C] Pittsburgh Compound B Positron Emission Tomography (PET-PiB) allow identification of individuals who are asymptomatic but are at increased risk to develop clinically symptomatic AD. Preclinical AD can further be separated into various stages based on the severity of pathology[15]. In addition to having abnormal A$\beta_{1–42}$, stage 2 preclinical AD includes biomarker evidence of neuronal injury and stage 3 also includes subtle cognitive decline. All preclinical AD stages are classified as cognitively normal by the Clinical Dementia Rating (CDR) of 0. There are several studies on the relationships between preclinical AD, depression, and biomarkers[11,16–18]. However, some studies historically excluded persons with depression or depressive symptoms because of concern for a confounding effect on cognition[19–22]. *A priori* exclusion of individuals based on depressive symptoms limits generalizability of results from studies of preclinical AD and cognition when it is unclear whether depression is indeed a confounding variable.

The primary aims of this cross-sectional study were to determine whether the presence of depressive symptoms has an effect on cognitive function in cognitively normal older adults, and to determine whether there is an interaction between preclinical AD and depression

status with regards to cognitive function, in a sample that includes patients with subsyndromal depressive symptoms and clinical depression. Secondary aims included studying the aforementioned relationships in a subset of participants with later-stage (stage 2 or 3) preclinical AD[15], and studying the influence of psychotropic medication treatment on amyloid burden and cognitive function, given studies that suggest protective effects of Selective Serotonin Reuptake Inhibitor (SSRI) usage on amyloid burden and cognitive function[23,24], and an increased risk of AD with benzodiazepine usage[25].

METHODS

Sample

Participants in this cross-sectional study were cognitively normal community-dwelling volunteers enrolled between November, 1997 and January, 2014, in longitudinal studies of memory and aging at the Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC), Washington University School of Medicine (St. Louis, MO, USA). Participants in the Knight ADRC cohort were living independently in the community at study entry and underwent annual clinical assessment unless prevented by death, illness, refusal, or relocation from the St. Louis area. Participants were selected for this study based on the following criteria: completion of cognitive, CSF and/or imaging, and clinical assessment protocols; CDR score of 0; at least 65 years of age at time of acquisition of biomarker data; and good general health. The Knight ADRC excludes possible participants with mood disorders only if they were hospitalized for depression or underwent electroconvulsive therapy (ECT) within the past five years of enrollment. Participants were not excluded based on the history of their mood severity, or if they have undergone ECT greater than five years prior to evaluation, and were not excluded after enrollment based on depression severity. The Human Research Protection Office at Washington University School of Medicine approved the studies. Written informed consent was obtained from all participants at enrollment.

Clinical assessments were conducted by experienced clinicians (physicians or advanced practice nurses) using independent semi-structured interviews with both the participant and a collateral source (typically the spouse or adult child of the participant). Information from the interviews permit rating of the presence or absence of dementia and, when present, its severity, with the CDR[26]. Psychometric testing[27] was completed within approximately 2 weeks after the clinical assessment. A CDR score of 0 indicates cognitive normality. Data were used from the assessment closest to the time of the biomarker studies for each participant.

Measures

Cognitive Assessment—Participants completed a 2-hour battery of standard paper and pencil cognitive measures, based on the Uniform Dataset (UDS) of the National Alzheimer's Coordinating Center[28], within approximately 2 weeks of clinical evaluation. Psychometrists were unaware of the results of the CDR or prior cognitive assessments. Knight ADRC's cognitive batteries have been described in detail in prior publications[29]. We constructed three domain-specific cognitive composite z-scores and a global cognitive composite z-

score, using means and standard deviations from healthy participants. The executive function domain included the Trail-Making Test Part A and Part B, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test, Block Design from the Wechsler Adult Intelligence Scale (WAIS); as well as the Digit Span forward and backward and Mental Control subtests from the Wechsler Memory Scale (WMS). The episodic memory domain included the Free and Cued Selective Reminding Test, the Associate Learning subtest from the WMS, and WMS-R Logical Memory. The language domain included the Boston Naming Test, category fluency for animals, and word fluency for the letters "S" and "P" (60 seconds allowed for each letter). The global cognitive composite included all of the above tests. Since processing speed is often impaired among individuals with depression[3–5], an exploratory composite was created using each measure that emphasizes performance speed. The speed composite included the Trail-Making Test Part A and Part B, WAIS-R Digit Symbol, WAIS Block Design, category fluency and word fluency.

Depressive symptoms—Three indexes of depressive symptoms were examined: clinician judgment of mood disorder at the conclusion of the clinical assessment with the participant and the collateral source, depressive symptoms reported by the participant, and depressive symptoms reported by the collateral source. All categories of active depression (e.g. unspecified depressive disorder, major depressive disorder, adjustment disorder with depressed mood, depression due to a general medical condition), with the exception of normal bereavement, were included in the diagnosis of active mood disorder[14]. This allowed the clinician to use clinical judgement based on the open-ended history gathered at the time of the assessment from the collateral source and the participant, a review of the depressive screening tools from both the collateral source and participant, and from the current mental status exam of the participant. The 15-question Geriatric Depression Scale (GDS)[30] was used to assess current depressive symptoms endorsed by the participant. Question 5a of the Neuropsychiatric Inventory Questionnaire (NPI-Q), asks the collateral source, "Does the patient act as if he or she is sad or in low spirits? Does he or she cry?" This was used to assess depressive symptoms from the collateral source[31]. In order to include the greatest number of participants with the widest range of depressive symptomatology, participants were classified as having depressive symptoms if they had clinician-rated active mood disorder, if the collateral source provided yes on question 5a of the NPI-Q, or if the participant's GDS score was greater than 4 out 15[32]. Thus the "depressive symptoms" group included participants with subsyndromal and clinical depression. The NPI-Q and GDS are included in the UDS.

Biomarker and imaging assessment—We used the cerebrospinal fluid (CSF) markers $A\beta_{1–42,}$ t-tau and $ptau_{181}$, as well as PET-PiB amyloid burden to define the presence of preclinical AD. The collection process has been described previously[15]. The mean cortical binding potential (MCBP) was used as the marker of amyloid burden from PET-PiB imaging, following protocols previously described[33]. The CSF and PET-PiB markers were dichotomized (normal or abnormal) by previously defined cutoffs for discriminating CDR 0 from CDR>0 (symptomatic AD). The optimal cutoffs for abnormal CSF markers were < 459 for $A\beta_{1–42}$, > 339 for t-tau, and > 67 for $ptau_{181}$ (all in pg/mL)[15]. The optimal cutoff for PET-PiB imaging was an MCBP value of > 0.18[34]. Participants were classified with

preclinical AD when having either an abnormal $A\beta_{1–42}$ concentration or an abnormal MCBP value. As a further analysis, we evaluated participants with later-stages of preclinical AD. Participants were classified with “stage 2 or 3” preclinical AD when having both an abnormal $A\beta_{1–42}$ value and an abnormal t-tau or $ptau_{181}$ value, reflecting neuronal injury[15]. Participants with possible stage 3 Preclinical AD, which includes subtle cognitive changes, were not assessed as a separate group, although all participants were CDR 0.

Medication usage—For an exploratory analysis of medication usage, we obtained current psychotropic medications typically used by individuals with depression from the participant’s medication list provided at the time of clinical assessment. These medications were then grouped according to class, including: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), benzodiazepines, monoamine oxidase inhibitors (MAOIs), sleep aids, and atypical antidepressants (Bupropion and Mirtazapine). Prescription medication usage is included in the UDS.

Statistical Analysis

Group comparisons with continuous variables were carried out with 2-sided *t* tests, and group comparisons with categorical data were analyzed with chi-square tests for all demographic variables. To test our primary aim while accounting for potential confounders, we created a linear model for each of the cognitive composites described above. Each composite was a separate dependent variable in a model that compared the dichotomized variables of preclinical AD status and the presence of depressive symptoms. The other covariates included in the final model were age at CSF collection, education level, apolipoproteinE ε4 *(APOE ε4)* status, and sex. The linear model was independently run using each definition of preclinical AD, as described above.

For exploratory analysis, the relationship between various categories of psychotropic medication usage and preclinical AD status was tested using logistic regression. Additionally, we created a linear model testing the effect of the use of benzodiazepines, SNRIs and SSRIs on cognitive function, and adjusting for the same potential confounders described above. TCAs, MAOIs, sleep aids and atypical antidepressants were not analyzed separately due to small sample sizes.

RESULTS

Sample Characteristics

Data were available for 356 participants meeting the inclusion criteria. 198 participants were initially excluded for having a CDR greater than 0. In relation to Lumbar Puncture (LP), individuals underwent a clinical assessment within an average of 80 days (*SD* = 78) and psychometric testing within an average of 59 days (*SD* = 80). Demographic data stratified by the presence of depressive symptoms and preclinical AD status, as defined by the presence of abnormal CSF $A\beta_{1–42}$ or PET-PiB, are shown in Table 1. Depressive symptoms were more common among females, consistent with known depression epidemiology[35]. Individuals with preclinical AD were older, had lower MMSE scores, and were more likely

to carry at least one copy of *APOE* ε4. When "preclinical AD" was defined as being both CSF $A\beta_{1–42}$ and tau positive, the new "Stage 2 or 3 preclinical AD" cohort (n = 41) did not differ significantly from the previously described cohort in any of the demographic variables. Psychotropic medication usage was reported in 94 participants; the most common medication classes were SSRIs (n = 49), SNRIs (n = 11) and benzodiazepines (n = 26).

Of participants in the group with depressive symptoms (N=54), fifty-six percent had a clinician diagnosis of active mood disorder, forty-eight percent had a positive NPI-Q, and thirty-one percent had a positive GDS. Additionally, sixty-one percent of participants in the group with depressive symptoms had an active psychotropic medication prescription. However, the severity of depressive features in this cohort was mild (mean GDS score = 3.1, *SD* = 2.3). Of participants in the preclinical AD group, seventy-seven percent had abnormal $A\beta_{1–42}$ levels, forty-three percent had an abnormal PET-PiB result, and nineteen percent with both modalities evaluated had concordant abnormal results. Forty-two percent of participants with abnormal CSF $A\beta_{1–42}$ levels also had abnormal tau levels.

Influence of Depressive Symptoms and Preclinical AD on Cognitive Function

The covariates of age, education and sex affected several cognitive domains, while *APOE* ε4 status did not have an effect. Prior to stratification of participants into biomarker positive and negative cohorts, there was no association between depressive symptoms and cognitive function. When defined by an abnormal biomarker result from either neuroimaging or CSF assay, our linear model yielded no significant relationships between the presence of depressive symptoms and cognitive performance (Table 2a). There were also no significant relationships regarding processing speed, the exploratory composite. While there was a significant negative relationship between the presence of preclinical AD and executive function (−0.17, 95% CI: −0.33, −0.01) and a nearly significant relationship between the presence of preclinical AD and global cognitive function (−0.13, 95% CI: −0.26, 0.01), there were no interactive effects between the presence of depressive symptoms and preclinical AD.

We also sought to assess these relationships in the context of more advanced stages of preclinical AD, including Stage 2 or 3 preclinical AD, in accordance with a hypothesized staging system[15] (Table 2b). As expected, participants with greater disease burden (as defined by the presence of the neuronal injury marker, tau, in addition to amyloid), demonstrated poorer function in the domain of episodic memory (−0.50, 95% CI: −0.76, −0.23), as well as global cognitive function (−0.25, 95% CI: −0.42, −0.07). Interestingly, there was an interactive effect of stage 2 or 3 preclinical AD on the relationship between the presence of depressive symptoms and both episodic memory (0.96, 95% CI: 0.31, 1.62) and global cognitive function (0.46, 95% CI: 0.028, 0.89). This represents a significantly negative association between depressive symptoms and these cognitive domains in the context of later-stage preclinical AD, and suggests that the presence of depressive symptoms may indeed be a late prodrome of AD.

Associations Among Medication Usage, Preclinical AD, and Cognitive Function

Preclinical AD status was unrelated to the use of SSRIs (OR: 1.62, 95% CI: 0.75, 3.50), SNRIs (OR: 0.51, 95% CI: 0.06, 4.35) or benzodiazepines (OR: 0.36, 95% CI: 0.10, 1.32). Adjusting for covariates, SNRI usage had a negative relationship with global cognitive function (−0.34, 95% CI: −0.67, −0.02), but no other significant relationships were found.

DISCUSSION

We examined the relationship between preclinical AD pathology, depressive symptoms, and cognitive functioning in cognitively normal older adults and found no associations of depressive symptoms on cognitive functioning in participants with either no or Stage 1 Preclinical AD. However, in later-stage (Stage 2 or 3) preclinical AD, there was an interactive effect on the relationship between depressive symptoms and the global and episodic memory cognitive domains. This supports the concept that depressive features may be a late prodrome of symptomatic AD, as these interactive effects appear only in later stage preclinical AD.

The present study may help clarify conflicting research regarding the relationship between depressive symptoms, AD, and cognitive function. While studies have suggested that depressive symptoms may be a prodrome of AD[9], there have been no studies to date that have employed biomarker evidence to support this claim. In some LLD studies, depression predicted poorer cognitive performance in several domains in non-demented individuals[3–5]. These studies also lacked the specific biomarker testing employed in the present study. One prosepctive study that longitudinally followed the relationship between brain amyloid burden and depressive symptoms found modest effects on depression severity, but excluded patients with clinical depression and did not stratify by preclinical AD stage[22]. One study that assessed participants with mild AD dementia concluded that, while some cognitive tests were modestly correlated with depressive features (possibly due to Type I error), the presence of depressive features had no overall association with cognitive performance beyond the effect of dementia[14]. Our study draws similar conclusions in a cognitively normal cohort, while also including a subanalysis of participants with markers of neuronal injury, which may be key to more comprehensively understanding the complicated relationship between depression and preclinical AD. Overall, there is no study to our knowledge that assesses the various interactions between multiple stages of preclinical AD, depressive symptoms (including clinical depression), and cognitive function across multiple domains.

In previous studies, psychotropic SSRI usage was shown to decrease cortical amyloid-β levels using PET-PiB[23] and CSF amyloid-β levels[36], whereas benzodiazepine usage has been associated with an increased risk of AD[25]. However, in accordance with existing studies[13,17], we did not find psychotropic medications to have an association with amyloid burden. Similar to other studies[37], we found no effect of psychotropic medication usage on cognitive function. One exception was an unexpected negative relationship between SNRI usage and global cognitive function (−0.34, 95% CI: −0.67, −0.02)[24]. Because a majority of participants with depressive symptoms reported use of psychotropic medications, this

secondary analysis provided at least some evidence that psychotropic medication use is not related to cognitive function.

Strengths of this study include the robust cognitive measures that are sensitive to asymptomatic disease and subtle changes in mood, the use of multiple modalities to assess preclinical AD, and the analysis of concurrent psychotropic medication use. Additionally, this study had wide inclusion criteria in regard to the severity of depression. Of the individuals categorized as having depressive symptoms in our study, nearly half (n = 25) had depressive symptoms as determined by the GDS or NPI-Q but did not have a clinician diagnosis of active mood disorder, thus including participants with subsyndromal depression, which is prevalent among older adults[6]. The remaining participants (n = 29) where characterized as having a clinician diagnosis of active mood disorder, unlike similar studies that excluded such participants at enrollment[11,22]. After enrollment, the Knight ADRC did not remove participants based on depression severity or treatment unless the participant or collateral source requested termination of participation due to severe medical or psychiatric illness.

There are also several limitations to consider. The number of participants with depressive symptoms was relatively small (n = 54). Also, the severity of depressive symptoms was relatively low (mean GDS 3.1, *SD* = 2.3), potentially reducing the sensitivity of any observed effect of severe depression on cognitive function. While our participants are generally healthy and highly educated[38], severe systemic and psychiatric illnesses are known to influence mood, cognition and behavior. While there is no evidence from the present study that participants with depression of any severity should be excluded, this study is unable to comment on the most severely depressed individuals that may have chosen or were unable for logistical reasons to be able to participate.

Also, our study was cross-sectional, as we used participant data from the visit closest to the biomarker studies, thus limiting our ability to claim causality of these relationships. The number of prior visits was not accounted for and may have a minor effect on cognitive performance[39]. While there was insufficient longitudinal follow-up to assess true progression to dementia, the use of CSF biomarkers and PET-PiB imaging is a commonly used way to assess the presence of preclinical AD[15,33,34]. Additionally, the clinical diagnosis of depression was not always made precisely on the day of cognitive testing, but rather within two weeks due to logistical challenges. Given the short timeframe between clinician diagnosis and psychometric testing, this discrepancy is unlikely to significantly confound our results. Finally, in regard to our secondary analysis with psychotropic medications, we were unable to assess compliance, duration or number of psychotropic medications used, which may have affected our power to observe meaningful associations between psychotropic medication usage and cognition. Future studies on this population may prospectively study psychotropic usage and effects of cognitive decline over time.

CONCLUSION

This study may help clarify the conflicting findings regarding the relationship between LLD, cognitive function, and neurodegenerative illnesses such as AD. The interactive effects

between depressive symptoms and cognition seen only in the later stages of Preclinical AD supports the idea that depressive features may be a late prodrome of symptomatic AD. Additionally, studies investigating cognitive function in older adults may not need to exclude participants with depressive symptomatology, but may still consider depressive symptoms as a potential confounder in the context of more extensive neuronal injury.

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Table 1

Table 1a. Sample Characteristics with Comparisons of Depression status[a]

	Depressive symptoms (n = 54)	No depressive symptoms (n = 300)
Age, y (SD)	71.37 (5.40)	72.48 (5.47)
Education, y (SD)	15.00 (2.73)	15.75 (2.80)
MMSE, score[b] (SD)	28.78 (1.53)	28.86 (1.36)
GDS (SD)	3.06 (2.33)*	0.73 (0.96)
Sex, % female	70.4*	50.3
APOE ε4, % positive	31.5	35.3

Table 1b. Sample Characteristics with Comparisons of Preclinical AD status

	Preclinical AD status[c]		Stage 2 or 3 Preclinical AD status[d]	
	Biomarker positive(n = 107)	Biomarker negative (n=249)	Biomarker positive(n = 47)	Biomarker negative (n=309)
Age, y (SD)	74.94 (6.49)*	72.09 (5.49)	75.69 (5.95)*	72.53 (5.84)
Education, y (SD)	15.93 (3.09)	15.47 (2.83)	14.91 (2.68)	15.67 (2.85)
MMSE, score[b] (SD)	28.61 (1.50)*	29.07 (1.19)	28.57 (1.61)*	28.95 (1.28)
GDS (SD)	0.99 (1.23)	0.96 (1.40)	1.04 (1.20)	1.03 (1.49)
Sex, % female	49.5	55.8	51.1	57.0
APOE ε4, % positive	49.5*	27.3	53.2*	31.5

[a] Two participants were not included due to missing information.

[b] Scored 1–30; 30 is a perfect score.

[c] Preclinical AD here represents an abnormal biomarker result from PET-PiB neuroimaging, or CSF assay (using only abnormal $A\beta_{1-42}$ as a cutoff), or both, in cognitively normal persons.

[d] Stage 2 or 3 Preclinical AD represents both abnormal $A\beta_{1-42}$ and tau levels

* $P < 0.01$, compared to the group with no depressive symptoms (table 1a) or no preclinical AD (table 1b)

Abbreviations: MMSE, Mini-Mental Status Exam; *APOE* ε4, ApolipoproteinE ε4.

Table 2a.

Effect of depressive features and preclinical AD[a] on cognitive performance.

	Depressive symptoms		Preclinical AD		Interaction[b]	
	Regression Coefficient	95% CI[c]	Regression Coefficient	95% CI[c]	Regression Coefficient	95% CI[c]
Executive Function	−0.06	−0.28, 0.15	−0.17*	−0.33, −0.01	0.24	−0.19, 0.68
Episodic Memory	−0.04	−0.31, 0.23	−0.13	−0.33, 0.08	0.25	−0.28, 0.79
Language	−0.06	−0.32, 0.20	−0.04	−0.24, 0.16	0.23	−0.30, 0.77
Global	−0.06	−0.23, 0.12	−0.13	−0.26, 0.01	0.25	−0.11, 0.60
Processing Speed	−0.17	−0.38, 0.05	−0.12	−0.28, 0.04	0.35	−0.08, 0.79

Table 2b.

Effect of depressive features and Stage 2 or 3 preclinical AD[d] on cognitive performance.

	Depressive symptoms		Stage 2 or 3 Preclinical AD[a]		Interaction[b]	
	Regression Coefficient	**95% CI[c]**	**Regression Coefficient**	**95% CI[c]**	**Regression Coefficient**	**95% CI[c]**
Executive Function	−0.01	−0.22, 0.19	−0.19	−0.41, 0.04	0.13	−0.41, 0.67
Episodic Memory	−0.09	−0.34, 0.15	−0.50*	−0.76, −0.23	0.96*	0.31, 1.62
Language	−0.09	−0.33, 0.16	−0.12	−0.39, 0.15	0.62	−0.04, 1.28
Global	−0.05	−0.21, 0.11	−0.25*	−0.42, −0.07	0.46*	0.03, 0.90
Processing Speed	−0.13	−0.34, 0.07	−0.16	−0.38, 0.06	0.44	−0.10, 0.98

[a] Preclinical AD defined as abnormal CSF $A\beta_{1–42}$ or PET-PiB (n = 354).

[b] Interaction between depressive symptoms and preclinical AD for each cognitive domain

* $p < 0.05$

[c] 95% CI = 95% Confidence Interval.

[d] Stage 2 or 3 Preclinical AD represents both abnormal $A\beta_{1–42}$ and tau levels (n = 47).