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Depression is Associated with Tau and Not Amyloid Positron Emission Tomography in Cognitively Normal Adults

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Abstract

Background: Depression is also common with older age. Alzheimer's disease (AD) studies suggest that both cerebrospinal fluid and positron emission tomography (PET) amyloid biomarkers are associated with more depressive symptoms in cognitively normal older adults. The recent availability of tau radiotracers offers the ability to examine *in vivo* tauopathy. It is unclear if the tau biomarker is associated with depression diagnosis.

Objective: We examined if tau and amyloid imaging were associated with a depression diagnosis among cognitively normal adults (Clinical Dementia Rating = 0) and whether antidepressants modified this relationship.

Methods: Among 301 participants, logistic regression models evaluated whether *in vivo* PET tau was associated with depression, while another model tested the interaction between PET tau and antidepressant use. A second set of models substituted PET amyloid for PET tau. A diagnosis of depression (yes/no) was made during an annual clinical assessment by a clinician. Antidepressant use (yes/no) was determined by comparing medications the participants used to a list of 30 commonly used antidepressants. All models adjusted for age, sex, education, race, and

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apolipoprotein [H9255]4. Similar models explored the association between the biomarkers and depressive symptoms.

Results: Participants with elevated tau were twice as likely to be depressed. Antidepressant use modified this relationship where participants with elevated tau who were taking antidepressants had greater odds of being depressed. Relatedly, elevated amyloid was not associated with depression.

Conclusions: Our results demonstrate that tau, not amyloid, was associated with a depression diagnosis. Additionally, antidepressant use interacts with tau to increase the odds of depression among cognitively normal adults.

Keywords

Alzheimer's disease; antidepressants; biomarkers; depression; older adults

INTRODUCTION

Symptomatic Alzheimer's disease (AD) is the sixth leading cause of death in the United States and is projected to increase to 14 million cases by 2050 [1]. Although cognitive impairment and decline are hallmark characteristics of symptomatic AD, neuropsychiatric symptoms (e.g., apathy, agitation), and mood disorders are also common sequelae [2]. Specifically, depression is common among older adults and is especially prevalent among persons with symptomatic AD. In community samples of healthy older adults, depression ranges from 15 to 20%, but increases to over 25% in symptomatic AD [3, 4]. A recent meta-analysis found the pooled prevalence of depression is higher (32%) in persons with mild cognitive impairment [5]. Depression is both a risk factor for AD, as well as a consequence of symptomatic AD. However, the issue of causality remains unclear [6].

The availability of biomarkers like positron emission tomography (PET) allows for *in vivo* evaluation of amyloid and tau, and examination of resulting pathology in a cognitively normal individual. Current research has shifted to focusing on preclinical AD to examine the prevalence and relationship between biomarkers and depression. AD biomarkers include cerebrospinal fluid (CSF) amyloid- β ($A\beta_{42}$), total tau (t-tau), and phosphorylated tau (ptau₁₈₁), and PET imaging using Pittsburgh Compound B (PIB)/florbetapir (AV45) for amyloid and flortaucapir (AV1451) for tau. A number of studies have assessed the relationship between depression, amyloid, and tau biomarkers. A 2015 systematic review examined associations between depression (symptoms or clinical diagnosis) and amyloid in older adults. In this meta-analysis, 15 out of 19 studies found differences in amyloid levels between depressed and non-depressed older participants [7]. Five studies used *in vivo* amyloid (PiB, AV45), four studies used CSF $A\beta_{42}$, while the remaining studies used serum and plasma markers of $A\beta_{40-42}$. The association with depression did not differ across amyloid measurement across the three methodologies. However, considerable variability existed in the assessment and diagnosis of depression across studies. Cognitive function was evaluated by screening measures (e.g., Mini-Mental State Examination, MMSE) in a majority of the studies instead of a neuropsychological battery. Given the ceiling effects of the MMSE, it is unclear how subtle cognitive impairment may have influenced the

depression-amyloid relationship. Another systematic review and meta-analysis examined the role of CSF tau and ptau₁₈₁ biomarkers among persons with late life major depressive disorder and healthy controls, and found no group differences in CSF tau or ptau₁₈₁ levels [8]. The majority of the studies included in both reviews were cross-sectional in design and did not have a representative sample of age-ranges.

However, several cohort-based studies have also examined the longitudinal relationships between depressive symptoms and AD biomarkers among cognitively normal older adults as defined by a Clinical Dementia Rating (CDR) of 0. In a small sample ($n = 66$) of CDR 0 older adults from the Knight Alzheimer Disease Research Center (ADRC), participants with higher PET amyloid levels and higher CSF ratio tau/A β ₄₂ at baseline developed more depressive symptoms as measured by a change score in the Geriatric Depression Scale (GDS) over one year, compared with participants with lower biomarker levels [9]. The specific findings between depressive symptoms (GDS) and *in vivo* amyloid (PET-PIB) were replicated in 270 cognitively normal older adults from the Harvard Aging Brain Study (HABS) who were followed over five years [10]. Similar results were also observed in the Australian Imaging Biomarkers and Lifestyle (AIBL) cohort ($n = 359$) where elevated PET amyloid was associated with more depressive symptoms (GDS) over four and a half years. These studies primarily focused on PET amyloid and did not use more recently developed PET tau methods. With the availability of PET tau radiotracers, including ¹⁸F-AV-1451 [11], we can study the relationship between tauopathy and depression. One recent pilot study of cognitively normal older adults ($n = 111$) from the HABS cohort, found a modest association between depressive symptoms and PET tau in the inferior temporal lobe [12]. These studies provide valuable insight into the potential associations between AD biomarkers and depressive symptoms but did not control for the possible effects of antidepressants on this relationship.

In general, antidepressant use tends to be greater in persons with AD [13]. One meta-analysis of five studies from over 4,100 studies screened, found antidepressant use was associated with a two-fold higher risk of cognitive impairment or dementia, irrespective of age [14]. Age was highlighted to be a potential modifier since adults who were prescribed antidepressant treatment before the age of 65 had a higher risk (three-fold) of having some form of cognitive impairment. However, evidence from a retrospective study of cognitively normal participants (CDR = 0) with a history of depression found selective serotonin reuptake inhibitors were associated with reduced PET amyloid burden over five years [15]. In a randomized double-blind study ($n = 23$), the antidepressant citalopram was associated with a 38% reduction in concentration of CSF A β ₄₂ compared to placebo in healthy adults ages 21–50 suggesting a positive effect of antidepressant on reducing amyloid burden [16]. A recent review observed that the risk of developing AD may be reduced for cognitively normal persons with clinical depression who are treated with certain antidepressants for a prolonged period of time (>4 years). However, antidepressants may have a deleterious effect on the trajectory within individuals who already have cognitive decline due to AD [17]. Given the conflicting findings regarding antidepressants and AD, additional biomarker studies are needed to better understand the effects of antidepressants on AD onset and progression [17–19].

This cross-sectional study examines whether the presence of PET tau and/or amyloid positivity is associated with a depression diagnosis among cognitively normal participants across a spectrum of ages (46–91 years old). In addition, this study evaluates if an interaction occurs between antidepressant use and either PET biomarker and if they are associated with an active depression diagnosis. Finally, this study examines the relationship between tau and amyloid imaging biomarkers, along with depressive symptoms and neuropsychiatric symptoms. Based on the extant literature, we hypothesized that a depression diagnosis would be associated with more abnormal PET amyloid compared to PET tau, depression diagnosis would interact with antidepressant use and be associated with abnormal PET amyloid, and there would also be an association between PET amyloid and higher depressive symptoms.

METHODS

Inclusion criteria

Data were obtained from participants enrolled in studies conducted by the Knight ADRC at Washington University. Participants were cognitively normal as defined by the CDR which has been previously published [20]. At the Knight ADRC, participants annually complete a clinical and neurological exam, a health history, and neuropsychological assessments. Blood is collected annually, while biomarker testing (PET amyloid and tau imaging) is also obtained. All DNA samples are genotyped with the Illumina 610 or the Omniexpress chip to obtain Apolipoprotein ε genotype using previously described methodologies[21]. This study was approved by the Institutional Review Board of Washington University in Saint Louis, and all participants provided signed informed consent.

Depression evaluation and antidepressant use

A depression diagnosis (yes/no) was obtained from a clinician interview using Form D1: Clinician Diagnosis on the National Alzheimer's Coordinating Center's Uniform Data Set (NACC UDS)[22]. During the annual clinical assessment, self-reported inquiries were made regarding depression and psychiatric disorders (schizophrenia, anxiety, and bipolar), and whether these disorders were active, recent, or absent. Information from the participant's self-report along with information from the clinical interview were synthesized to determine if depression was present. The clinician made the final determination whether active depression was present or not. Medication use was derived from the NACC UDS[23] (Form A4 Subject Medications). A list cataloguing 30 active and discontinued antidepressants were evaluated and included selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), norepinephrine and dopamine reuptake inhibitors (NDRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAOI), and mixed 5-HT (e.g., noradrenergic and specific serotonergic antidepressant, serotonin antagonist and reuptake inhibitors). Medications that participants listed on Form A4 were cross-referenced with the list of available antidepressants to determine whether the participant was taking antidepressants.

Depression symptoms and neuropsychiatric symptoms

Participants completed the GDS [24], a 15-item screen for depression in older adults. Respondents answer “yes” or “no” for each item, with higher scores (range: 0–15) indicating greater depressive symptoms. A participant’s collateral source completed the Neuropsychiatric Inventory Questionnaire (NPI-Q), a 13-item clinical measure which examined the presence and severity of neuropsychiatric symptoms over the past month [25]. The score ranged from 0–39 with higher scores indicating increasing severity of neuropsychiatric symptoms.

Neuropsychological performance assessments

Participants annually complete a battery of neurological assessments, in addition to the CDR [20] and MMSE [26]. Based upon our prior study [27], four assessments were identified to be strongly predictive of cognitive impairment, and were sensitive to changes in cognition during the conversion from cognitively normality to symptomatic AD. These tests include, Animal Naming [28], Selective Reminding Test Free Recall (SRTFREE) and Cued subtests [29], and Trail Making (A and B tests) [30]. Higher scores on the Animal Naming and SRTFREE and lower scores on the Trail Making A and B indicated better performance. A preclinical Alzheimer cognitive composite (PACC) score was calculated where the aforementioned four measures were transformed into z scores and averaged.

PET tau imaging

Participants completed PET imaging to determine tau burden using the radiotracer [¹⁸F]-Flortaucipir (AV1451) in a Biograph mMR 124 scanner (Siemens Medical Solutions, Erlangen, Germany) based upon previously described methodology [31, 32]. Using a standard protocol, each participant was administered a single 6.5–10 mCi bolus of AV1451 infused over 20 s. Quantitative PET analysis used the 80–100-min post injection window for flortaucipir. PET tau data was processed using the PET Unified Pipeline (github.com/ysu001/PUP). FreeSurfer version 5.3 was used for segmentation of regions of interest (ROI), where a tissue mask was generated based on that segmentation for a region. Partial volume correction was performed. Regional target-to-reference intensity ratio, also known as the standard uptake ratio (SUVR) was evaluated for each region, using the cerebral cortex as the reference region. The partial volume corrected SUVR derived from cortical regions was used as a summary value for each ROI. A PET tau summary measure was derived using the arithmetic mean of the amygdala, entorhinal cortex, inferior temporal region, and lateral occipital cortex as defined by FreeSurfer. A summary score for the PET tau SUVR of 1.22 was deemed positive [33].

PET amyloid imaging

A previously described PET imaging protocol [32] was also completed for determining amyloid burden using the radiotracer [¹⁸F]-Florbetapir (AV45). Each participant was administered a single 7.4–11.3 mCi bolus of AV45. Partial volume corrected SUVRs were calculated for ROIs with the cerebellum used as a reference region. A summary score for the PET amyloid SUVR of 1.19 was deemed positive [31, 32, 34].

Statistical analysis

Differences in demographics for depressed versus non-depressed were examined using descriptive statistics. Tau and amyloid imaging biomarker variables were dichotomized based on established cutoffs as described above for all analyses. Based on the NACC UDS, depression diagnosis and antidepressant use from the annual assessment closest to tau imaging (two years prior or six months after) were both dichotomized as present or absent. Age and education were continuous variables measured in years. Sex (male/female), race (white/nonwhite), and having at least one copy of the *APOE4* allele (no/yes) were dichotomous. Logistic regression examined whether depression is associated with PET tau while controlling for age, sex, education, race, and *APOE4* status. A separate logistic regression model examined whether depression is associated with the interaction between PET tau and antidepressant. These two models were re-run substituting PET tau for PET amyloid. To examine impact of both tau and amyloid pathology on depression, we combined both biomarkers and created a categorical variable (e.g., Tau –, Amyloid –; Tau –, Amyloid +; Tau +, Amyloid –; Tau +, Amyloid +). In order to examine potential differences on depressive symptoms as a continuous variable (measured via GDS), a general linear model was fitted to analyze group differences separately for PET tau and PET amyloid, while adjusting for the prior covariates. The same model was used for examining neuropsychiatric symptoms as a continuous variable (measured via NPIQ). To examine cognitive performance via neuropsychological assessments, a general linear model was fitted to analyze group differences, separately for tau and amyloid biomarkers on the PACC score, while adjusting for the same covariates. The default, force entry method was used for logistic regression. Collinearity diagnostics and residual analysis were used to determine the final model did not violate the assumptions of linearity, independence of errors and multicollinearity. Analyses were conducted in SPSS version 25 (Chicago, IL, USA).

RESULTS

Participant demographics are presented in Table 1. Participants ranged in age from 46 to 91 years old, were highly educated, were more likely female, and were primarily Caucasian. SUVRs for PET tau and amyloid as well as predicted probability were plotted as a function of depression diagnosis (Fig. 1). When examining PET tau (normal/elevated) alone, 40% of these cognitively normal participants had elevated tauopathy. Similar examination of PET amyloid (normal/elevated) found about 24% had elevated amyloid. However, this distribution changed when PET tau and PET amyloid were combined (Table 1). More than half the sample had no evidence of preclinical AD, roughly a quarter were classified as suspected non-Alzheimer disease pathology (SNAP) due to positive PET tau only [35–37], approximately eight percent were only PET amyloid positive, while nearly 16% were both PET amyloid and PET tau positive.

Based on annual evaluation, 12% of the cohort had depression. Participant self-report of depressive symptoms was low with scores ranging from 0–10, with 80% scoring 0 or 1 on the GDS. However, persons with depression had higher scores on the GDS ($M = 2.71$, $SD = 2.68$) compared to those without depression ($M = 0.62$, $SD = 0.90$) and they were significantly different ($p = 0.001$). Relatedly, the collateral source report of participant's

neuropsychiatric symptoms ranged from 0–9 with 87% scoring 0 or 1 on the NPIQ. There were no differences between those without depression compared to those with depression with regards to age, education, race, or *APOE4*. However, there was a difference in sex ($\chi^2 = 8.44$, $p = 0.004$) with a higher percentage of women (79%) depressed compared to men (21%). Finally, in chi-square analyses, there was a statistically significant difference for PET tau with respect to depression ($\chi^2 = 7.48$, $p = 0.006$) where depressed participants had an elevated PET tau level compared to non-depressed individuals. However, there was no difference in PET amyloid deposition with regards to depression ($\chi^2 = 0.723$, $p = 0.395$). When the relationship between biomarkers and antidepressant use was examined, participants who were prescribed antidepressants had elevated PET tau ($\chi^2 = 9.64$, $p = 0.002$) compared to individuals who were not taking antidepressants. There were no differences between participants who were and were not prescribed antidepressants and PET amyloid ($\chi^2 = 0.02$, $p = 0.882$).

In a logistic regression model that adjusted for tau, age, education, race, sex, and *APOE4* status, depression was predicted by PET tau, where a participant with an elevated PET tau was twice as likely to have a depression diagnosis (Table 2). Sex was the only statistically significant demographic predictor, with males having a lower odds of depression compared to females. A secondary model examined the effect of antidepressants and the interaction between PET tau and antidepressant use. The interaction term was statistically significant in the model, suggesting participants taking antidepressants and who had elevated PET tau deposition were more likely to be depressed (Table 2). The main effect of antidepressant use was statistically significant but PET tau and sex were not.

We also studied the relationship between PET amyloid and depression. Overall, PET amyloid was not associated with depression in this sample (Table 2). In a secondary model that examined the interaction between PET amyloid and antidepressant use, neither the interaction term nor PET amyloid were significant; however, antidepressant use remained as a significant main effect. The final model examined if PET tau and PET amyloid combined as categorical variables for different biomarker groups (Table 3) were associated with depression, while adjusting for demographic variables. The overall biomarker group variable was not a significant predictor. Based on these null results, testing the effect of antidepressant use and the interaction between antidepressants with the biomarker groups was conducted and also found to be not significant. However, we specifically examined the combined impact of both elevated levels of tau and amyloid (~16%) and did not find participants with both pathologies having increase odds for depression. While the overall variable was not significant, the SNAP group (Tau +, Amyloid-; 24%) was approaching statistical significance ($p = 0.060$), suggesting participants in the SNAP group had a higher odds for depression.

In the general linear models adjusting for demographic covariates, there were no statistically significant differences between biomarker groups (normal/elevated levels) on depressive symptoms using GDS for either PET tau ($p = 0.418$) or PET amyloid ($p = 0.567$) or in neuropsychiatric symptoms for either PET tau ($p = 0.678$) or PET amyloid ($p = 0.241$). When neuropsychological performance was examined via the PACC score, there were no significant group differences between depression (yes/no), antidepressant use (yes/no), PET

tau (normal/elevated), or PET amyloid (normal/elevated). When the PACC score was added to the models presented in Table 2, the PACC variable was not a statistically significant predictor in any of the four models (all p 's > 0.50).

DISCUSSION

In a sample of cognitively normal adults, we found that depression was associated with PET tau, where elevated levels of tau deposition more than doubled the odds of having a depression diagnosis. When antidepressant use was included in the model, an interaction between tau and antidepressant use was observed which further increased the odds of depression. Furthermore, we did not observe a significant relationship between PET amyloid and depression even after including the interaction between antidepressant use and PET amyloid. These results did not support our hypothesis of associations between depression, antidepressants, and PET amyloid.

The most notable finding is that tau, not PET amyloid, was associated with depression. This result is partially supported with the recent AD biomarker literature, which demonstrates a lack of a relationship between PET amyloid and depressive symptoms in cross-sectional analyses in cohort studies [9, 10, 38]. The association between tau and depression is further supported when both biomarkers were grouped and approximately 25% of the sample were categorized as SNAP. However, 42% of the participants with depression were classified in the SNAP group suggesting an increased presence of a mood disorder like depression may be a non-cognitive characteristic of SNAP. A recent study of healthy older adults ($n = 573$) in the AIBL cohort found a similar prevalence of SNAP (~22%), and when compared to those without preclinical AD (Tau –, Amyloid–), the SNAP group had lower cognitive scores and hippocampal volume but showed no decline in either outcome over six years[39]. However, that study did not examine depression or neuropsychiatric symptoms as an outcome. Another study using the HABS cohort also found a comparable prevalence of 26% with SNAP among 247 cognitively normal older adults (CDR = 0) with age ranging from 63–90 [40]. Similar to the AIBL cohort, that study did not examine depression or neuropsychiatric symptoms. We were unable to find other studies using SNAP participants to support or refute this finding. Future longitudinal studies are needed to follow SNAP participants and determine how many of those with SNAP convert to also having amyloidosis.

Another reason for these findings may be explained by limited power in the PET amyloid models where only 24% of the sample had elevated levels of amyloid compared to 40% for tau. Additionally, the 40% for PET tau positivity may seem more elevated when compared to PET amyloid, despite both being based on established cutoffs. Sample size in prior AD biomarker studies [41–43] estimate 22–37% of cognitively normal older adults have preclinical AD; however, this prevalence may vary depending on use of biomarker and/or tracer type, single or combinations of biomarkers, the cut-off score indicating positivity, and framework/classification systems [44–46]. Given the nascency of PET tau and its recent implementation in many cohorts, studies are needed to confirm and replicate the prevalence of tau positivity and sensitivity using similar brain regions [47].

These results also recapitulate prior work, which demonstrated that both depressive symptoms (GDS) and neuropsychiatric symptoms (NPIQ) were not associated with AD biomarkers (PET amyloid) cross-sectionally [9]. This finding may reflect the overall physical and mental health of the participants who are cognitively normal older adults (CDR 0), highly educated, and reported minimal depressive and neuropsychiatric symptoms. Rather, participants with elevated levels of amyloid tend to experience changes in depressive symptoms (higher) over time. These longitudinal associations between PET amyloid and depressive symptoms were recently replicated with the HABS [10] and AIBL cohorts [38] with larger samples and longer follow up times. Our results demonstrated no cross-sectional relationship between depressive and neuropsychiatric symptoms and AD biomarkers with PET tau imaging.

Antidepressant use is expected to be strongly associated with depression simply because people on antidepressants are more likely to take them due to depression compared to other uses (e.g., chronic pain, migraine). A model examining depression using antidepressant medication as a predictor with the same covariates, but without tau, found that medication was statistically significant ($p = 0.001$; OR = 27.6; 95% CI 10.4–73.0). The finding of antidepressants impacting the relationship between tau and depression was not surprising in this cognitively normal sample of adults. There were 35 participants on an antidepressant without a depression diagnosis and 30 taking an antidepressant with depression. However, the interaction between antidepressants and tau suggests that participants taking antidepressants and with elevated tau levels had a greater odds of depression. This may be also interpreted as tau modifying the association between antidepressant use and depression. Participants taking SSRIs and SNRIs were more likely to have elevated tau. This result is partially supported by studies that found antidepressant use were associated with cognitive impairment in older adults [14, 48]. However, these studies did not have biomarkers to confirm the role of antidepressants on preclinical AD nor did they have a sample of cognitively normal adults. While cross-sectional analyses in this study could not determine causality, it is very likely that depressed participants taking antidepressants contributed to more elevated tau deposition. Another explanation for this finding may be due to depression severity where persons with depression who were taking antidepressants were more depressed (e.g., GDS score) than those with depression who were not taking antidepressants. Longitudinal studies are needed to examine whether specific classes of antidepressants increase cerebral tau deposition.

The results did not find age, race, or education to be related to depression although there was an association with sex. Men were less likely to be depressed compared to women. This finding is consistent with the literature showing higher prevalence rates of depression (symptoms and diagnosis), awareness and admitting, and seeking treatment for women compared to men [49–51]. Additionally, there were no differences in neuropsychological performance as reflected by the PACC score when examined across PET amyloid or tau (normal/elevated) or by depression diagnosis (yes/no). As discussed in the introduction, antidepressant use is associated with a higher risk of cognitive impairment, as evaluated by screens (e.g., MMSE). While there was not a statistically significant difference on PACC for antidepressant use (yes/no), the difference was marginally significant ($p = 0.065$) with those taking antidepressants having a higher PACC score suggesting better cognitive performance.

These findings suggest that cross-sectional assessment of cognitive functioning, among a cognitively normal sample (CDR 0) may not accurately reflect changes in the ongoing neurodegenerative process of AD or identify differences in depression.

There are some limitations to this study that may lead to differences in what other studies report. Given the cross-sectional nature of this design, and use of archival data, it is difficult to determine causal nature of depression and AD biomarkers. Depression diagnosis could include those with current or recent depression. However, the diagnosis was not operationalized using a systematic or uniform criterion like the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition or other specific psychiatric exclusions. Additionally, the data were unable to differentiate depression subtypes (major depression, bipolar depression, dysthymia, etc.), new onset versus life-long depression or provide detail about age of onset, number of depressive episodes, and severity. Moreover, we could not identify how clearly antidepressants modified the relationship between AD biomarkers and depression. It is possible that other conditions like pain, anxiety, or sleep disorder may have impacted these results. The antidepressants captured on Form A4 (subject medication) excluded specific information relating to prescription, dosage, frequency, and potential drug interactions with other medications. Additionally, some older antidepressants like tricyclics and monoamine oxidase inhibitors were not captured. The lack of statistically significant findings between the GDS and NPIQ with the biomarkers may be due to sensitivity issues or use of a self-report/informant report as an invalid measure when compared to a clinical assessment. PET radiotracers type, dosage, and cutoff for positivity are normed on the Knight ADRC cohort. We were unable to test whether antidepressant use was associated with worsening depression over time. While the PACC assessed cognitive functioning, we did not examine subjective cognitive decline. Finally, our sample included a large proportion of Caucasians, who were well educated, most lacking significant physical disabilities, psychiatric, or neurologic conditions/diagnosis, which may not be representative of the general population. As a result, findings may not be easily generalizable to the larger population.

Taken together, these findings suggest that cerebral tau pathology, not amyloid, were associated with depression among cognitively normal adults with women having a higher odds compared to men. Additionally, antidepressant use and elevated tau levels suggested an increased odds of depression among adults. It remains unclear whether depression is a risk factor or a consequence of symptomatic AD; however, these results suggest that preclinical AD as reflected by PET tau may be associated with active depression among cognitively normal participants. The lack of group differences on a neuropsychological composite suggest that cognitive decline is not affected in this relationship. Future longitudinal studies are needed to examine how conversion from preclinical to symptomatic AD, as measured by PET tau, is impacted by lifelong versus new-onset of depression, the emergence of depressive symptoms in the preclinical stage of AD, and the role of specific classes of psychotropic medications in this relationship.

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Fig. 1.
Predicted probability of PET tau and PET amyloid standard uptake ratios plotted as a function of depression diagnosis.

Table 1**Demographics (N = 301) ***

Age (y)	69.5 ± 8.0
Education (y)	16.3 ± 2.3
Women, N (%)	172 (57.0%)
Race, Caucasian, N (%)	266 (88.4%)
<i>APOE4</i> , N	99 (32.9%)
MMSE (out of 30)	29.3 ± 1.1
PACC score	-0.48 ± 0.49
Antidepressant use, N (%)	65 (21.6%)
Classes N (%)	
None	236 (78.4%)
NDRI	16 (5.3%)
SSRI	19 (6.3%)
SNRI	18 (6.0%)
Two or more	12 (4.0%)
<u>Outcomes</u>	
Depression, N (%)	38 (12.6%)
GDS	0.88 ± 1.4
NPIQ	0.55 ± 1.3
<u>Biomarker status (%)</u>	Non-Depressed (n = 263) Depressed (n = 38)
Tau – Amyloid –	142 (54.0%) 15 (39.5%)
Tau – Amyloid +	23 (8.7%) 0 (0.0%)
Tau + Amyloid –	57 (21.6%) 16 (42.1%)
Tau + Amyloid +	41 (15.6%) 7 (18.4%)

MMSE, Mini-Mental State Examination; PACC, Preclinical Alzheimer Cognitive Composite; SUVR, Standardized Uptake Value Ratios; GDS, Geriatric Depression Scale; NPIQ, Neuropsychiatric Inventory Questionnaire; NDRI, norepinephrine–dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors.

* Mean±Standard Deviation or count (percentage).

Table 2
Association between depression and biomarkers among cognitively normal participants

	<i>p</i>	OR	95% CI	
			Lower	Upper
Model 1a				
Tau (Ref = Negative)	0.021	2.42	1.14	5.14
Age (y)	0.520	0.985	0.941	1.03
Education (y)	0.409	0.936	0.800	1.09
Race (Ref = Other)	0.451	1.64	0.454	5.90
Sex (Ref = Female)	0.025	0.382	0.164	0.886
<i>APOE4</i> (Ref = no)	0.114	0.514	0.225	1.17
Model 1b				
Tau (Ref = Negative)	0.207	0.252	0.030	2.15
Age (y)	0.613	0.986	0.934	1.04
Education (y)	0.188	0.878	0.724	1.07
Race (Ref = Other)	0.435	0.534	0.110	2.58
Sex (Ref = Female)	0.310	0.600	0.224	1.61
Antidepressant use (Ref = No)	0.001	8.51	2.50	28.9
Tau-Antidepressant X	0.018	17.9	1.63	198.2
<i>APOE4</i> (Ref = no)	0.076	0.386	0.135	1.10
Model 2a				
Amyloid (Ref = Negative)	0.584	0.766	0.294	1.99
Age (y)	0.896	1.01	0.958	1.05
Education (y)	0.419	0.938	0.803	1.09
Race (Ref = Other)	0.374	1.79	0.496	6.44
Sex (Ref = Female)	0.006	0.315	0.138	0.718
<i>APOE4</i> (Ref = no)	0.307	0.644	0.276	1.50
Model 2b				
Amyloid (Ref = Negative)	0.997	0.000	0.000	–
Age (y)	0.883	0.996	0.946	1.05
Education (y)	0.196	0.883	0.732	1.07

	<i>p</i>	OR	95% CI	
			Lower	Upper
Race (Ref = Other)	0.405	0.530	0.119	2.36
Sex (Ref = Female)	0.270	0.580	0.211	1.53
Antidepressant use (Ref = No)	0.000	20.9	7.65	57.5
Amyloid-Antidepressant X	0.997	5.8e7	0.000	–
<i>APOE4</i> (Ref = no)	0.303	0.588	0.214	1.61

OR, odds ratio; CI, confidence interval; X, interaction; Ref. reference category.

* Degrees of freedom for all models = 1.

Table 3
Biomarker groups associations with depression among cognitively normal participants

	<i>p</i>	OR	95% CI	
			Lower	Upper
Model 3a				
Biomarker groups (Ref = Tau – Amyloid –)	0.301			
Tau – Amyloid +	0.998	0.000	0.000	–
Tau + Amyloid –	0.060	2.17	0.968	4.86
Tau + Amyloid +	0.284	1.82	0.607	5.51
Age (y)	0.706	0.991	0.945	1.04
Education (y)	0.432	0.938	0.801	1.10
Race (Ref = Other)	0.381	1.76	0.492	6.41
Sex (Ref = Female)	0.029	0.390	0.167	0.908
<i>APOE4</i> (Ref = no)	0.190	0.557	0.232	1.34

OR, odds ratio; CI, confidence interval; X, interaction; Ref, reference category.

* Degrees of freedom for all models = 1.