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Temporal associations of neuropsychiatric symptoms, demographics and amyloid with subsequent tau burden in older adults

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ABSTRACT

Background: Psychiatric symptoms are increasingly recognized as early manifestations of Alzheimer's disease (AD). These symptoms may reflect or contribute to underlying neurobiological changes, including tau burden, which represents more advanced AD pathology. Understanding factors associated with tau burden may help identify individuals at elevated risk and improve early detection strategies.
Objectives: To investigate the temporal relationships between neuropsychiatric symptoms, demographic factors, and tau burden, by examining amyloid (Aβ)-dependent, -independent, and interactive associations.
Design: Retrospective cohort study.
Setting: Alzheimer's Disease Neuroimaging Initiative.
Participants: We included 681 participants without dementia (mean age = 71.2 years, 51.8 % female).
Measurements: The participants underwent tau PET scanning with prior amyloid PET and Neuropsychiatric Inventory (NPI) interview assessments clustered around three time periods relative to tau PET: closest (0 − 2 years), mid (3 − 5 years), and furthest (6 − 8 years). Linear regression analyses, adjusting for age and APOE ε4 alleles, examined associations of NPI scores, sex, education, and their Aβ-status interactions with tau burden.
Results: Higher total NPI scores up to 2 years prior to tau PET were associated with greater tau burden independently of Aβ status, whereas anxiety symptoms demonstrated an Aβ-dependent relationship with tau. (*NPI: β=0.117, 95 % CI: 0.049 to 0.185, $p = 0.001$*, Anxiety: *β=0.249, 95 % CI: 0.073 to 0.424, $p = 0.006$*). NPI measured up to 5 years prior to tau PET interacted with Aβ on tau burden (0–2 years: *β=0.272, 95 % CI: 0.136 to 0.407, $p < 0.001$,* 3–5 years: *β=0.336, 95 % CI: 0.127 to 0.544, $p = 0.002$*). Sex and education showed minimal associations with tau at uncorrected statistical levels.
Conclusions: Neuropsychiatric symptoms were associated with tau burden up to two years before tau sampling, independently of Aβ, and interacted with Aβ status up to five years prior, suggesting that neuropsychiatric symptoms are related to tau in the short term and may represent manifestations of advancing AD pathology. Demographic factors showed minimal associations. These findings highlight the importance of evaluating neuropsychiatric and anxiety symptoms as potential indicators of increased tau pathology.

1. Introduction

Given the importance of treating individuals as early as possible in the Alzheimer's disease (AD) process, there has been a growing emphasis on enrolling cognitively unimpaired (CU) individuals in clinical trials based on their positive amyloid-beta (Aβ) status [1]. However,

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this approach runs the risk of including individuals who may not be at high risk of developing cognitive decline in the near future.

This challenge stems from the differential relationships between AD pathologies and clinical outcomes. While cognitively unimpaired individuals can often present with a significant Aβ PET burden, it is less likely that they display an extensive pattern of tau-PET deposition [2]. Indeed, clinical symptoms are more closely related to the location and extent of tau PET uptake rather than Aβ PET [2–4]. Therefore, identifying factors that associate with advanced tau pathology, including in the context of existing Aβ, is essential for designing successful clinical trials and developing preventive interventions [5].

Factors influencing AD progression can be conceptualized as either modifiable or non-modifiable. Among non-modifiable factors, evidence suggests that sex influences AD pathology. Cognitively unimpaired females exhibit higher tau pathology compared to males, as evidenced by tau PET imaging [6,7] and post-mortem studies [8], while most studies have not found sex differences in Aβ levels measured by PET [7] or CSF [9]. Among modifiable factors, which offer potential intervention opportunities, higher education has been linked to lower Aβ in cognitively unimpaired older adults [10,11]. Similarly, neuropsychiatric symptoms, apart from being potential risk factors for AD progression [12], are also increasingly recognized as early manifestations of AD [13]. However, their role as early markers of pathophysiological progression in AD remains still somewhat unclear. Current evidence suggests neuropsychiatric symptoms may emerge at multiple stages of the AD *continuum*, with distinct temporal patterns for different symptom types. Depression, anxiety, and sleep disturbances can become prevalent in preclinical AD, while others, such as hallucinations and disinhibition, may manifest at later stages once AD diagnosis is established [14]. Symptoms of depression and anxiety have been observed in cognitively normal older adults with higher Aβ levels [15,16]. However, the strongest associations appear to emerge as tau pathology develops, with neuropsychiatric symptoms showing more consistent relationships with tau burden in AD-vulnerable brain regions in the inferior temporal and entorhinal cortex independent of Aβ pathology [17]. Similarly, various other neuropsychiatric symptoms have been associated with elevated tau PET levels across the AD *continuum* [18]. Importantly, studies suggest that neuropsychiatric symptoms may accelerate AD progression [19,20], highlighting the importance of identifying them.

Beyond these individual effects, emerging evidence suggests that both modifiable and non-modifiable factors may interact with Aβ to predict tau burden. For example, Aβ-positive women show higher tau-PET deposition in medial and inferior-lateral temporal regions compared with Aβ-positive men [21], and individuals carrying the APOE ε4 allele have an increased tau load in AD-vulnerable brain areas compared with non-carriers [22]. Similarly, among modifiable factors, Aβ-positive individuals with lower stress-coping abilities exhibited higher levels of tau [23], suggesting that psychological factors may modulate tau pathology in the presence of existing Aβ burden.

Building on this research, our primary objective was to examine the temporal dynamics of study-partner reported neuropsychiatric symptoms and demographic factors with future tau burden across three time windows (0–2, 3–5, and 6–8 years) prior to tau acquisition in individuals without dementia, considering Aβ-dependent, -independent and interactive effects. This approach allows to shed light on the temporal ordering of these relationships by comparing associations across different time intervals, which could aid in designing successful interventions and trials to delay AD progression [24].

Based on previous evidence, we propose three hypotheses: (i) neuropsychiatric symptoms (total, anxiety, sleep disturbances and depression) will show stronger associations with concurrent tau burden (0–2 years) compared to long- term tau burden (3–8 years). This temporal pattern would be consistent with hypotheses suggesting that tau pathology and neuropsychiatric symptoms emerge concurrently; (ii) Aβ status will moderate the relationship between neuropsychiatric symptoms and tau burden, such that the neuropsychiatric symptom-tau associations will be stronger in the presence of existing Aβ pathology; (iii) female sex will exhibit higher tau burden and sex and education will interact with Aβ status on tau burden.

2. Methods

2.1. Study design and participants

We conducted a retrospective analysis using longitudinal data (between 2015–2023) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (ClinicalTrials.gov registry numbers: ADNI GO: NCT01078636 (registration date: 2010–03–02); ADNI 2: NCT0123197 (registration date: 2010–11–01); ADNI 3: NCT02854033 (registration date: 2016–08–03). The ADNI is a public-private longitudinal multicenter study aimed at developing biomarkers for the early detection and tracking of AD. Initiated in 2004, ADNI has significantly advanced AD research by facilitating global data sharing among researchers. Its primary objectives include early detection of AD, supporting interventions at pre-dementia stages, and maintaining an open data-access policy (www.adni-info.org). The inclusion and exclusion criteria of ADNI can be found in the ADNI protocol (adni.loni.usc.edu).

For this study, we included 681 (427 cognitively unimpaired and 254 MCI) participants who met the following criteria: available cross-sectional tau PET data, and retrospective longitudinal data on Aβ PET and NPI. Participants could not have a diagnosis of dementia at the time of their first Aβ PET. Additionally, all participants provided demographic information such as sex and years of education, and underwent genetic testing for the APOE ε4 genotype when they were enrolled in ADNI. Information about the participant selection process can be found in the supplementary material (Figure S1).

For each participant, we selected their latest available tau PET scan, which served as the reference point for our analysis. This maximized the backward time window, giving us more historical data, ensuring the most complete information available per participant. This single tau scan was the outcome of our subsequent analyses. Then we grouped the data into three time windows: 0–2 years, 3–5 years, and 6–8 years prior to the tau scan. If a participant had two or more visits within a time window, the one closest to the tau sample was used (Figure S2). The length of the time windows was chosen to maximize data availability and to approximate the average duration of clinical trials and intervention studies (~2 years) [25,26], making our findings more applicable to real-world intervention planning. For each window, we tested whether NPS, sex and education were associated with later tau pathology. We also examined whether amyloid status influenced these associations and whether amyloid interacted with NPS, sex and education.

All methods and protocols followed ADNI's ethical guidelines, which follow the standards of the institutional and/or national research committees as well as the 1964 Helsinki declaration and its later revisions. The ADNI study was approved by the institutional review boards of all the participating institutions. Written consent was obtained from all participants at each site before they were included. More details can be found at adni.loni.usc.edu. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. PET imaging and processing

Participants' scans were acquired between 2015 and 2023. Details about the acquisition and analysis of [18]F-Florbetapir (FBP), and [18]F-Flortaucipir (FTP) images can be found at [27]. The PET images were pre-processed following ADNI guidelines. In brief, images were aligned, averaged, and reoriented before being interpolated to a standardized image and voxel size (160 × 160 × 96 dimensions, with each voxel measuring 1.5 × 1.5 × 1.5 mm in x, y, z). They were then smoothed to achieve a uniform 8 mm resolution at full width at half maximum. Regional Standardized Uptake Value Ratios (SUVRs) for both FTP and

FBP were calculated by normalizing the regional uptake to a reference region.

FTP PET images were acquired in four 5-minute frames between 50–70 min after injection (10.0 mCi ±10 %). The reference region used was the inferior cerebellum [28]. Continuous SUVRs from the composite Braak regions I/II, which represent the earliest stages of neurofibrillary tangle formation in the brain [2], were used as outcome.

FBP PET images were acquired in four 5-minutes frames between 75–105 min after injection (10 mCi ±10 %). The reference region used was the whole cerebellum 29. The global SUVR was calculated using a composite region that included the frontal, parietal, cingulate, and temporal regions [30]. The SUVRs were then converted into Centiloid units by linear transformation using the PET tracer equations published for conversion [31]. Due to data distribution, subjects were then classified as Aβ positive or negative using 20 CL as threshold [32].

2.3. Neuropsychiatric symptoms and cognitive evaluation

All participants' study-partners underwent the Neuropsychiatric Inventory interview, which is a reliable tool for assessing psychopathology [33]. It is based on interviews with qualified study partners to assess both the frequency and severity of symptoms such as delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability, apathy, and aberrant motor behavior. ADNI addressed potential bias from responses from relatives by conducting an interrater reliability assessment across various domains, confirming and maintaining an excellent level of agreement [34]. The NPI demonstrates satisfactory validity and reliability in outpatient settings, with strong content validity across all items and acceptable concurrent validity when compared to standard instruments for assessing NPS in neurologically impaired patients [35]. The total NPI score, which ranges from 0 to 144, is the sum of all scores from the individual domains. In our study, we focused on the total NPI score and sub-scores for depression [36], anxiety [37] and sleep as key predictors, as these have been linked to AD pathology or are considered risk factors for AD.

Since the sub-scores for anxiety, sleep, and depression did not follow a normal distribution and showed limited variability (see Figure S3), we converted these variables to ordinal binary variables (1 for those with a score equal or higher to one; 0 for those with a score equal to zero), while the total NPI score was treated as a continuous variable.

2.4. Demographic and genetic data

The demographic variables included in the study were sex (female/male), and years of education (continuous variable). *APOE* genotyping was performed at the time of participant enrollment, where they were genotyped using DNA extracted by Cogenics from a 3 mL aliquot of EDTA blood. The genetic covariate included was the number of APOE ε4 alleles (0/1/2 as categorical ordered variable).

2.5. Statistical analyses

Demographic data were summarized as means (and standard deviations) for continuous variables and frequencies (and percentages) for categorical variables. Linear regression models were conducted to examine the association of tau burden in Braak I/II with total NPI score, depression, anxiety, sleep, sex, and years of education i) dependently, ii) independently and iii) in interaction with Aβ status, adjusting for sex, education, age and number of APOE ε4 alleles. Main and interaction effects were considered significant at $p < 0.05$ after correction for multiple comparisons with Bonferroni [38].

The outcome variable used in the different linear models was tau burden in the Braak I/II region. The exposures were Aβ status (positive/negative); NPI total scores; NPI sub-scores: anxiety, depression and sleep; sex; and years of education. Age, sex, education and APOE ε4 allele were considered in all the models. We tested the main effect of each variable of interest, the main effect of the variables of interest independent of Aβ status, and the interaction between the variable of interest and Aβ status.

Models used:

$$BraakI/IISUVR \sim Age + APOE + education + sex + exposure \quad (1)$$

$$BraakI/IISUVR \sim Age + APOE + education + sex + A\beta status + exposure \quad (2)$$

$$BraakI/IISUVR \sim Age + APOE + education + sex + A\beta status + A\beta status * exposure \quad (3)$$

All models were run using exposures and Aβ-PET data from different time windows (0–2 years, 3–5 years, and 6–8 years before tau PET scans) to examine how predictors at specific time points were associated with tau burden. Since education and sex are time-invariant, we opted to run models 1 and 2 for these variables using only the largest sample size available (i.e., closest time window). To examine whether amyloid positivity was driving any interactions in model 3, we additionally ran model 1 stratified by amyloid status.

Further, we performed a *post-hoc* analysis to investigate whether neuropsychiatric symptoms (total NPI score) mediate the relationship between Aβ status and tau burden. Specifically, we conducted mediation analyses across the three time windows, estimating the Average Causal Mediated Effect (ACME), Average Direct Effect (ADE), total effect, and proportion mediated. A nonparametric bootstrap procedure with 1000 simulations was used to derive 95 % confidence intervals and p-values. Mediation was considered significant at $p < 0.05$. These analyses were performed using the R package *mediation*.

All analyses were conducted using R (version 4.2.2).

3. Results

A total of 681 participants were included. At the time of their first amyloid-PET, 427 participants were cognitively unimpaired and 254 had mild cognitive impairment (MCI). The mean age at baseline was 71.2 (SD = 6.71), 51.8 % of the participants were females and 36.4 % had at least one APOE ε4 allele. The mean Mini Mental State Evaluation (MMSE) score was 28.7 (SD = 1.52) and the mean years of education was 16.5 (SD = 2.48). Demographic data for baseline and all time windows are shown in Table 1. Further information about the change in NPI status and diagnosis between time windows can be found in supplementary materials (Table S1).

Fig. 1 shows a summary of all the results from all the statistical analyses performed. The exact statistical values for these models can be found in supplementary materials (Table S2). Furthermore, for the sake of completeness, we are providing the statistical models with other neuropsychiatric symptoms in supplementary materials (Tables S3, S4 and S5).

3.1. Association of neuropsychiatric symptoms and demographics with tau burden

Below, we summarize the findings from model 1, where we explored the associations between neuropsychiatric symptoms, sex and education with tau burden across the three previously defined time windows (Fig. 1, first column).

We found that, after adjusting for age, sex, education and APOE ε4 carrier status, NPI total score (Fig. 2a) and anxiety (Fig. 2b) were significantly associated with tau burden only in the closest time window (*NPI total score. 0–2 years: $\beta = 0.150$, 95 % CI: 0.079 to 0.221, $p < 0.001$; Anxiety. 0–2 years: $\beta = 0.249$, 95 % CI: 0.073 to 0.424, $p = 0.006$*).

Further, we also observed that females showed higher tau burden compared with males at an uncorrected level (*$\beta = 0.172$, 95 % CI: 0.026*

Table 1
Demographic and clinical characteristics at baseline (first amyloid sample) for the participants included in the study.

	Baseline (First amyloid sample)	
	mean (SD) / count (%); range	N
Age	71.2 (6.71); (49.1–88.6)	681
Sex		681
Male	328 (48.2 %)	
Female	353 (51.8 %)	
Number of APOE ε4 alleles		681
0	433 (63.6 %)	
1	210 (30.8 %)	
2	38 (5.6 %)	
Diagnosis		681
CN	427 (62.7 %)	
MCI	254 (37.3 %)	
AD	0 (0.0 %)	
Education (years)	16.5 (2.48); (0–20)	681
NPI		
NPI total	2.21 (4.47); (0–43)	681
Depression (negative)	586 (86.2 %)	
Anxiety (negative)	629 (92.5 %)	
Sleep (negative)	564 (82.9 %)	
MMSE	28.7 (1.52);(9–30)	681
Race		681
American Indian or Alaskan Native	2 (0.3 %)	
Asian	11 (1.6 %)	
Black or African American	33 (4.9 %)	
White	622 (91.3 %)	
More than one race	12 (1.8 %)	
Unknown	1 (0.2 %)	
Time between amyloid and tau (months)	48.9 (44.9); (0–96)	681

Note1. APOE4: number of alleles (0, 1 or 2). CN: Cognitively normal. MCI: Mild-Cognitive Impairment. NPI total: Neuropsychiatric Inventory total score. Education: measured in years of education. MMSE: Mini Mental State Examination. Baseline: time when participants were enrolled in ADNI.
Note2. The possible range for NPI total score is 0–144. The possible range for MMSE is 0–30.
Note 3. Data for each time window included in supplementary material (Table S8).

to 0.318, $p = 0.021$, Uncorrected; Figure S4). No significant association was found with years of education.

3.2. Amyloid-independent associations of neuropsychiatric symptoms and demographics with tau burden

Here, we report the results corresponding to model 2, which builds on model 1 by additionally adjusting for Aβ-status (Fig. 1, second column).

After adjusting for Aβ-status, the association between the NPI total score at the closest time window and tau PET remained unchanged (*0–2 years: $\beta = 0.117$, 95 % CI: 0.049 to 0.185, $p = 0.001$*). However, the association of anxiety with tau was attenuated and did not reach anymore significance. Similarly, the association between female sex and tau burden was not anymore significant after adjustment for Aβ-status. Education remained non-significant.

3.3. Interaction of neuropsychiatric symptoms and demographics with amyloid to explain tau burden on early tau accumulation regions

This section presents the results corresponding to model 3, which examines the interactions between neuropsychiatric symptoms, sex and education with Aβ-status on tau burden (Fig. 1, third column).

Regarding neuropsychiatric symptoms, we found that in the two closest time windows, NPI total score interacted with Aβ-status (*Interactions: 0–2 years: $\beta = 0.272$, 95 % CI: 0.136 to 0.407, $p < 0.001$; 3–5 years: $\beta = 0.336$, 95 % CI: 0.127 to 0.544, $p = 0.002$;* Fig. 3). Stratified analyses by Aβ status (Fig. 4) showed that, among Aβ positive participants, a higher NPI total score was associated with higher tau burden (Figure S4, Table S6a).

Similarly to NPI total score, sleep disturbances interacted with Aβ-status, although at an uncorrected level (*Interactions: 0–2 years: $\beta = 0.298$, 95 % CI: 0.059 to 0.538, $p = 0.015$, Uncorrected; 3–5 years: $\beta = 0.481$, 95 % CI: 0.116 to 0.845, $p = 0.010$, Uncorrected*). Stratified analyses showed that among Aβ negative participants, sleep disturbances were associated with lower tau burden (Figure S5, Table S6b).

Regarding sex and education, Aβ-status interacted with both variables at an uncorrected level (*Interaction for sex: 3–5 years: $\beta = 0.428$, 95 % CI: 0.061 to 0.795, $p = 0.022$, Uncorrected; Interaction for education: 0–2 years: $\beta = -0.163$, 95 % CI: −0.300 to −0.028, $p = 0.018$, Uncorrected*). Stratified analyses showed that female sex was associated with higher tau burden among Aβ positive participants (Figure S6) while higher education was associated with higher tau burden among Aβ negative participants (Figure S7).

We further conducted a mediation analysis testing the mediating role of neuropsychiatric symptoms on the association between Aβ status and tau burden. Results revealed a significant mediation effect in the 0–2 year window, with neuropsychiatric symptoms accounting for approximately 3 % of the effect of Aβ on tau (*ACME = 0.02, 95 % CI: 0.00 to 0.07, $p = 0.032$; ADE = 0.74, 95 % CI: 0.57 to 0.91, $p < 0.001$; total effect = 0.76, 95 % CI: 0.59 to 0.94, $p < 0.001$; proportion mediated = 0.03, 95 % CI: 0.00 to 0.08, $p = 0.032$*; Table S7a). No significant mediation was observed in the remaining time windows (Tables S7b and S7c).

3.4. Sensitivity analyses

We conducted two sensitivity analyses to ensure the robustness of our findings. First, to ensure that our findings were not influenced by variability among the different samples used in each time window, we limited the sample to participants who had data at both the closest- and mid-time windows. We did not consider the furthest time window to preserve statistical power. The associations observed in the full cohort for Aβ status-NPI interactions remained significant but attenuated slightly for the mid-time window (Figure S8). Associations of sex with tau and Aβ status-sleep and Aβ status-sex interactions became stronger in these analyses (Figure S8), while the associations of anxiety with tau burden and the Aβ status-education interaction attenuated to non-significant. All other results remained consistent (Figure S8).

In the second sensitivity analysis, we treated Aβ as a continuous variable instead of a binary variable (Aβ positive/negative). This approach aimed to more accurately capture the influence of Aβ burden. The only significant interactions with Aβ were: sex, education, and total NPI score, all observed in the closest time window (Figure S9).

4. Discussion

In this retrospective cohort study of older adults, we examined the temporal associations between neuropsychiatric symptoms, demographic factors, and tau burden across different time windows. Our findings partially supported our hypotheses and revealed several key patterns. We found evidence of (i) a short-term association of total neuropsychiatric symptoms with tau burden, with and without adjusting for Aβ status, and a short-term association of anxiety with tau burden when not adjusting for Aβ status; (ii) a short- to mid-term interaction of total neuropsychiatric symptoms with Aβ status on tau burden; (iii) low evidence for higher tau burden among females (only when not adjusting for Aβ-status and at uncorrected level); and low evidence for interactions of sex and education with Aβ status on subsequent tau burden (only at uncorrected levels).

Our first hypothesis regarding stronger associations between neuropsychiatric symptoms and tau burden over shorter time intervals was partially supported. Higher total NPI scores were associated with greater tau PET burden in early AD-affected areas within the 2-year window independent of Aβ-status. As expected, we did not observe associations beyond 2 years, suggesting that neuropsychiatric symptoms

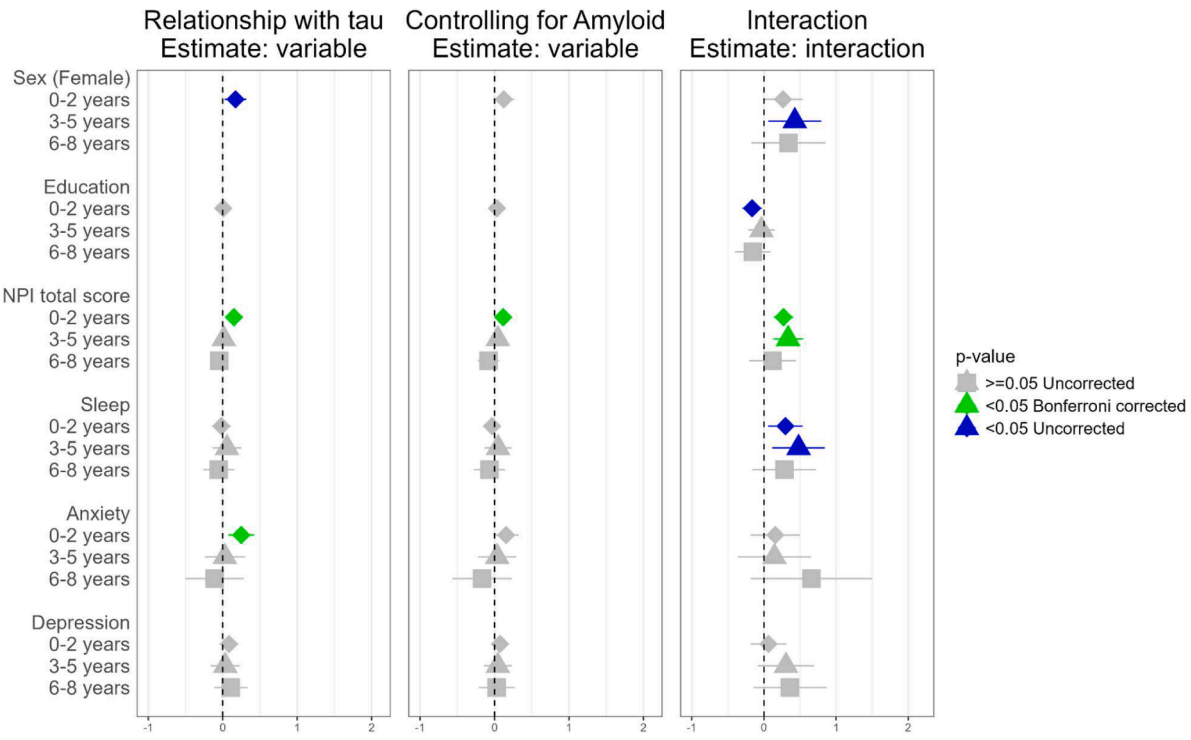

Fig. 1. Forest plot showing the association of neuropsychiatric and demographic variables with subsequent tau PET burden. First column shows results for model 1 (Braak I/II ~ exposure + covariates), second column shows results for model 2 (model 1 including additionally Aβ) and third column shows results for model 3 (model 2 including additionally the interaction Aβ*exposure).
Note. Estimates (and 95 % CIs) of demographics and NPI scores at different time windows on subsequent tau-PET SUVR. All models were adjusted for APOE4 alleles and age; when necessary, sex and education were also included as covariates. Color code: Blue: p-value below 0.05 uncorrected. Green: p-value below 0.05 Bonferroni corrected. Grey: p-value above 0.05.

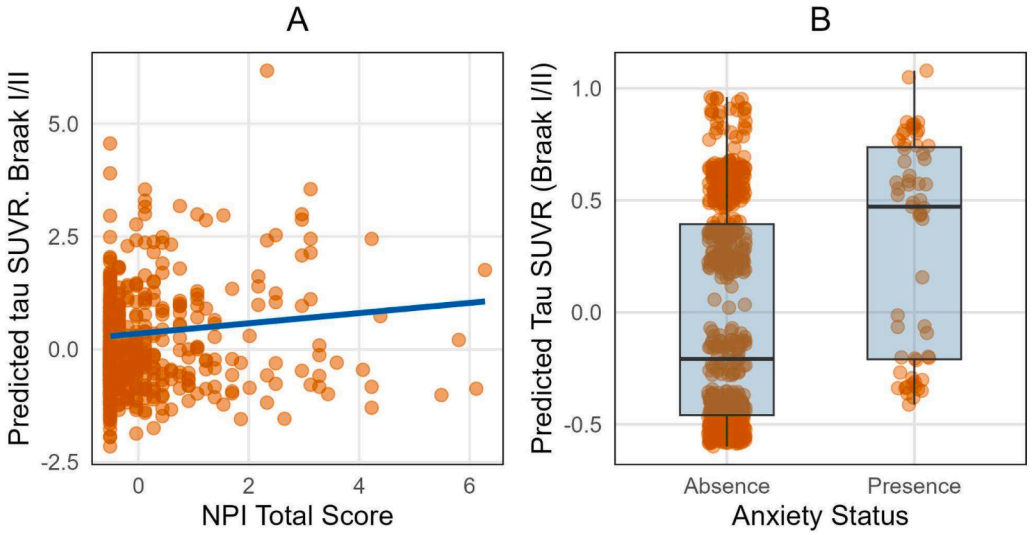

Fig. 2. Plots representing the association between tau PET SUVR in Braak I/II region neuropsychiatric symptoms in the 0–2 years time window. (A) Scatter plot representing the relationship between total NPI score and tau PET SUVR in Braak I/II. (B) Boxplot representing the association between Anxiety status and tau PET SUVR in Braak I/II.
Note: predicted values for tau PET SUVR were estimated from a linear regression model 1. Predictions were generated across the observed range of neuropsychiatric symptoms while holding covariates constant.

alone may not be a strong risk factor for AD pathology, like a clinical diagnosis of a psychiatric disease may be, as previous studies report an association between a previous depression diagnosis and higher AD risk [39]. The association within the 2-year window suggests neuropsychiatric symptoms may serve as early indicators of emerging tau pathology [40]. This interpretation is consistent with growing literature suggesting clinical manifestations and neuropsychiatric symptoms' close relationship with tau, particularly in early regions affected by AD [17,18,41], but little to no correlation with Aβ [18,42]. Our findings are also in line with those of a recent study [43] showing that neuropsychiatric burden increased across Braak stages, and that individuals at later Braak stages showed further increases in symptoms over a 2-year period. These

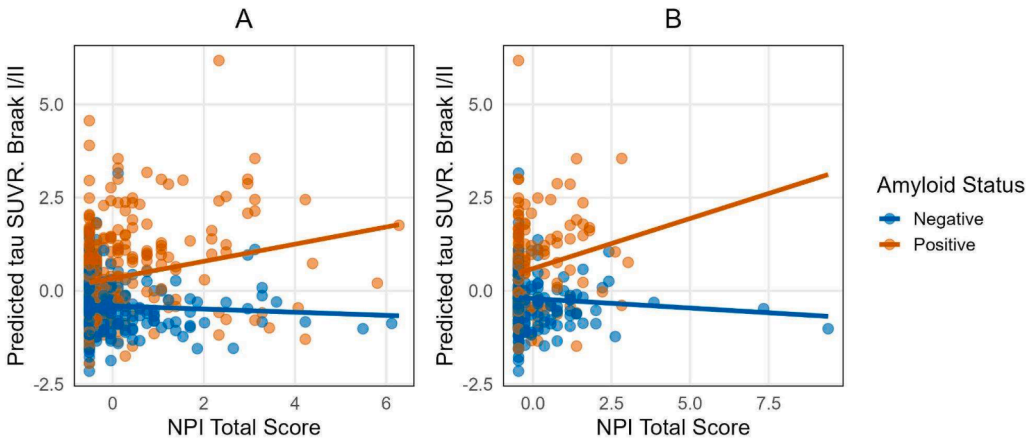

Fig. 3. Scatter plots representing interaction between NPI total score and Aβ status on tau PET SUVR measured in Braak I/II region (A) Represents interaction in the 0–2 years time window between NPI total score and Aβ status on tau PET SUVR measured in Braak I/II region; (B) represents the interaction in the 3–5 years time window between NPI total score and Aβ status on tau PET SUVR measured in Braak I/II region.
Note 1: to rule out the possibility that outliers were driving the interaction, we re-tested it after excluding NPI total values above 2.5 in *A−* individuals. The interaction remained significant. *Note 2:* predicted values for tau PET SUVR were estimated from model 3. Predictions were generated across the observed range of neuropsychiatric symptoms while holding covariates constant.

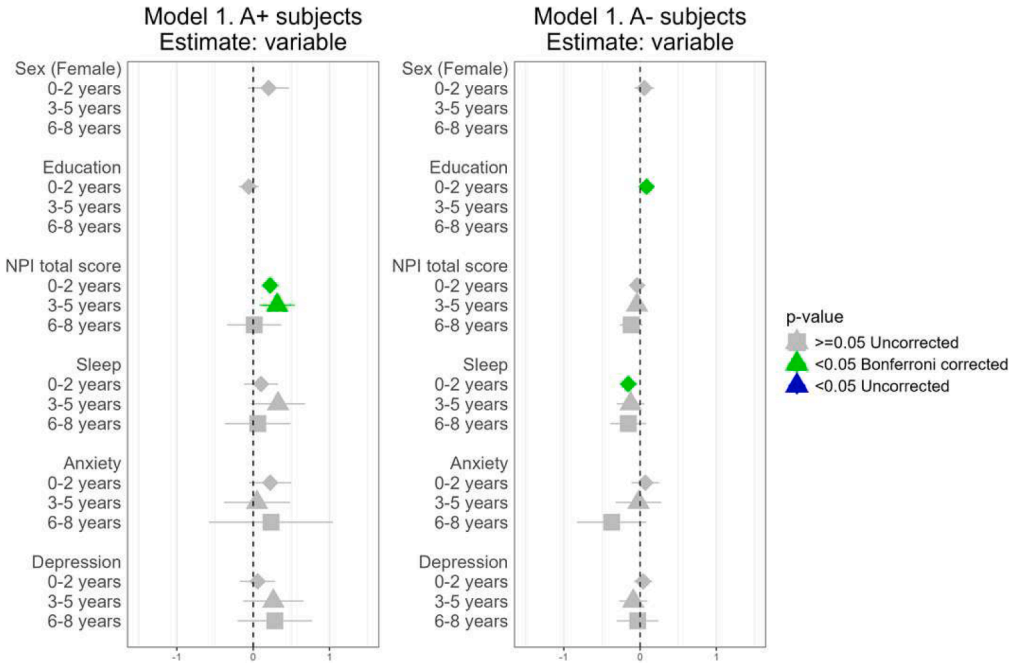

Fig. 4. Forest plot showing the association of demographic and neuropsychiatric variables with subsequent tau PET burden stratified by Aβ status (model 1). The first plot shows results for Aβ positive subjects. Second plot shows results for Aβ negative subjects.
Note. Estimates (and 95 % CIs) of demographics and NPI scores at different time windows on subsequent tau-PET SUVR. All models were corrected for APOE4 alleles and age, further in those necessary, sex and education was used as covariate as well. Color code: Blue: p-value below 0.05 uncorrected. Green: p-value below 0.05 Bonferroni corrected. Grey: p-value above 0.05

findings indicate that neuropsychiatric symptoms emerge early in the pathological process reflecting higher tau burden.

The emergence of neuropsychiatric symptoms concurrently with tau may reflect the neuroanatomical vulnerability of circuits involved in emotional regulation, particularly the entorhinal cortex and its connections with the limbic system and default mode network [41]. Such regions are implicated in both early tau deposition and in affective processing [41,44]. Potential mechanisms for the Aβ-independent association of tau burden with neuropsychiatric symptoms may include multiple pathways including neuroinflammatory processes, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and vulnerability of medial temporal lobe structures to both emotional dysregulation and tau spread. Specifically, neuropsychiatric symptoms and chronic stress may activate the HPA axis, leading to elevated glucocorticoids, such as cortisol. Elevated cortisol levels can directly promote tau hyperphosphorylation and aggregation, while also triggering neuroinflammatory cascades in tau-vulnerable regions [45]. Moreover, emotional processing networks may be preferentially susceptible to tau deposition independent of Aβ, consistent with studies reporting early tau in these regions in primary age-related tauopathy [46,47].

Among specific symptoms, anxiety showed associations with tau burden when not adjusting for Aβ-status within the 2-year window, aligning with previous findings of anxiety as an early AD manifestation [48,49]. However, these findings are not in line with those of a recent

meta-analysis among cognitively unimpaired individuals, reporting no association of anxiety symptoms with AD biomarkers [50]. However, interpretation requires caution given our use of informant reports, which may require higher symptom thresholds compared to self-report measures. Other specific symptoms, including sleep disturbances and depression showed no main effects on tau burden, contrary to some previous studies using self-reported measures [17]. For example, a cross-sectional study, conducted on the Harvard Aging Brain Study cohort including cognitively unimpaired individuals, reported a modest association of self-reported depressive symptoms (measured with the Geriatric Depression Scale) with tau PET burden in early tau areas [17]. Another cross-sectional study using the Framingham Heart Study cohort in cognitively unimpaired middle-aged participants, reported no association between self-reported depressive symptoms (measured with the Center for Epidemiological Studies Depression Scale) and tau PET uptake in the overall sample, but an association of depressive symptoms with entorhinal and amygdalar tau only among APOE ε4 carriers [51]. The mixed findings regarding depressive symptoms and tau PET might be explained by different scales (self-reported vs informant-based) used in studies or research design (longitudinal vs cross-sectional).

Our second hypothesis regarding Aβ-status moderation was supported within a 5-year window, where Aβ-positive individuals showed higher tau burden with higher neuropsychiatric symptoms compared to Aβ-negative individuals. This was further supported by the post-hoc mediation analysis suggesting that total neuropsychiatric symptoms partially mediated the relationship between Aβ-status and tau burden in the 0–2 years time window. While, to our knowledge, this is the first study examining such temporal relationships, previous studies have examined the interaction of NPS with Aβ on cognition, but not on tau. One recent study did not find NPS to moderate the relationship of Aβ with cognition cross-sectionally nor longitudinally [52], while another study showed higher Aβ to interact with NPS to accelerate cognitive decline [19]. Several interpretations of the interaction found in the current study are possible: (i) the co-occurrence of neuropsychiatric symptoms and Aβ positivity might identify individuals at a more advanced stage in the AD pathological continuum, (ii) Aβ pathology might increase vulnerability to stress-related factors, consistent with studies showing that Aβ-positive individuals with lower stress-coping abilities exhibit higher tau levels [23], or (iii) the presence of both neuropsychiatric symptoms and Aβ might synergistically relate to tau burden patterns.

We further found low evidence (at an uncorrected level) of an interaction of Aβ with NPI sub-variable of sleep, assessed within 5 years before tau PET. Previous literature has shown sleep to interact with AD pathology on cortical volume among ADNI participants [53]. Our findings extend this by demonstrating that sleep disturbances interact with Aβ status on tau burden, with Aβ negative individuals driving this interaction. It is therefore possible that sleep disturbances modulate the effects of metabolic dysfunction of Aβ and tau [54]. Future studies incorporating longitudinal tau PET imaging are needed to disentangle these potential mechanisms.

Contrary to our third hypothesis, sex and education showed limited associations with tau burden. Despite extensive literature demonstrating sex-related tau vulnerability, we only observed sex-differences at an uncorrected level, such that females, compared with males, exhibited higher tau burden, but only when Aβ-status was not adjusted for. Prior evidence shows that females exhibit higher tau pathology than males for equivalent cognitive performance [21,55,56]. This suggests that sex-related tau vulnerability may become more pronounced as cognitive decline emerges. We further observed an interaction at an uncorrected level of sex with Aβ status on tau burden, when Aβ was measured within 3 to 5 years before tau PET. These results serve as a replication of a previous study's finding using TRIAD and ADNI data, which showed a sex-specific modulation of cortical Aβ in tau phosphorylation among females across the clinical spectrum over time [57]. These sex-differences have been suggested to be explained by differential testosterone levels, protecting males against tau [58]. Our results, albeit weak, together with past literature suggest that, in general, females may have lower resistance to tau pathology which seems to be more driven by the presence of Aβ among females, compared with males.

Further, we found no main effects of education on tau burden. This is in line with previous studies indicating that years of education are associated with Aβ [11], but not consistently with tau [59]. However, we showed, at an uncorrected level, that Aβ and years of education measured within 2 years before PET assessment, interacted on tau burden. Stratified analyses revealed that this interaction may be driven by Aβ negative individuals, where higher educational attainment was associated with greater tau burden. While seemingly counterintuitive, this is consistent with recent findings reporting a similar association of higher education being associated with greater tau levels among Aβ-positive individuals [60]. This pattern may reflect education's role in cognitive reserve, whereby individuals with higher educational attainment may tolerate greater underlying pathology without clinical expression [61]. This finding may also reflect selection given our sample's high average educational attainment (mean = 16.5), or unmeasured socioeconomic or lifestyle factors that could promote tau accumulation (e.g., chronic occupational stress) associated with educational level. Overall, these results should be interpreted cautiously given the restricted educational variability of the sample, and warrant replication in future studies.

This study's strengths include the use of a longitudinal biomarker cohort employing standardized assessments; PET scan collection protocols and meticulous data quality control; and the large sample size allowing for interaction analyses, including both cognitively unimpaired and MCI participants. The study also has several limitations. We used complete-case data within our study resulting in different sample sizes and statistical power across the time windows, limiting the comparison of results across time windows. Although our sensitivity analyses matching participants from the closest and mid time windows showed consistency across results, we advise caution on drawing conclusions regarding the furthest time window. While the NPI has been considered a valid and reliable tool [62], it was originally designed for informant reporting by caregivers of AD patients. Recent validation studies across ADNI and NACC cohorts have, however, demonstrated its reliability in MCI populations, particularly through validated subscales measuring clinically meaningful symptom clusters [33,63]. However, its application to cognitively unimpaired individuals might introduce bias, as informants might require a higher threshold of symptom severity before reporting symptoms compared to self-report measures. While we addressed some measurement limitations by binarizing the sub-NPI variables to account for floor effects, future studies might benefit from complementing NPI with self-report measures in cognitively unimpaired individuals. Additionally, the NPI uses retrospective informant rating (preceding month), introducing potential recall bias. Further, as ADNI employs rigorous exclusion criteria, including the exclusion of participants with pre-existing depression, our study's sample is not representative of the general population. Finally, as 91.4 % of the participants included in our study were of White ethnicity, the results are not generalizable to other populations at risk. Future research will benefit from replicating these results in other populations, potentially using a combination of assessment tools to capture the full spectrum of neuropsychiatric symptoms across the cognitive *continuum*.

5. Conclusion

This study reveals important temporal relationships between neuropsychiatric symptoms and AD pathology in older adults. Higher neuropsychiatric symptoms showed associations with tau burden primarily within short time intervals (0–2 years), and this association was modified by Aβ status across short- and mid-term intervals (0–5 years). Among specific symptoms, anxiety was associated with tau burden only in models not adjusted for Aβ, while other symptoms, as well as sex and

education, showed weaker or non-significant associations. These temporal patterns suggest that neuropsychiatric symptoms might be concurrent manifestations of advancing AD pathology. Future longitudinal studies using both informant and self-report measures in diverse populations will be important for advancing our understanding of AD pathophysiology and developing more effective clinical strategies.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT and Claude in order to support the writing of this manuscript. This tool was used for language improvement, grammar correction, and suggestions on phrasing. After using these tools/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Pablo Aguilar-Dominguez: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Eleni Palpatzis:** Writing – review & editing, Writing – original draft, Conceptualization. **Muge Akinci:** Writing – review & editing. **Anna Canal-Garcia:** Writing – review & editing, Data curation. **Joana B. Pereira:** Writing – review & editing. **Alexandre Bejanin:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Eider M. Arenaza-Urquijo:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100294.

References

[1] Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? Sci Transl Med 2014;6(228). https://doi.org/10.1126/SCITRANSLMED.3007941.
[2] Jack CR, Wiste HJ, Botha H, et al. The bivariate distribution of amyloid-β and tau: relationship with established neurocognitive clinical syndromes. Brain 2019;142(10):3230–42. https://doi.org/10.1093/BRAIN/AWZ268.
[3] Ossenkoppele R, Schonhaut DR, Schöll M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139(5):1551–67. https://doi.org/10.1093/BRAIN/AWW027.
[4] Bejanin A, Schonhaut DR, La Joie R, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 2017;140(12):3286–300. https://doi.org/10.1093/BRAIN/AWX243.
[5] Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies. Neurology 2018;90(15):695–703. https://doi.org/10.1212/WNL.0000000000005303.
[6] Pereira JB, Harrison TM, La Joie R, Baker SL, Jagust WJ. Spatial patterns of tau deposition are associated with amyloid, ApoE, sex, and cognitive decline in older adults. Eur J Nucl Med Mol Imaging 2020;47(9):2155–64. https://doi.org/10.1007/S00259-019-04669-X.
[7] Arenaza-Urquijo EM, Boyle R, Casaletto K, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. Alzheimer's Dement 2024;19:27. https://doi.org/10.1002/ALZ.13844.
[8] Liesinger AM, Graff-Radford NR, Duara R, et al. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathol 2018;136(6):873–85. https://doi.org/10.1007/S00401-018-1908-X.
[9] Schoonenboom NSM, Pijnenburg YAL, Mulder C, et al. Amyloid β(1-42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. Neurology 2004;62(9):1580–4. https://doi.org/10.1212/01.WNL.0000123249.58898.E0.
[10] Gonneaud J, Bedetti C, Pichet Binette A, et al. Association of education with Aβ burden in preclinical familial and sporadic Alzheimer disease. Neurology 2020;95(11):e1554. https://doi.org/10.1212/WNL.0000000000010314.
[11] Arenaza-Urquijo EM, Bejanin A, Gonneaud J, et al. Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: neuroimaging evidence for protection and compensation. Neurobiol Aging 2017;59:72–9. https://doi.org/10.1016/J.NEUROBIOLAGING.2017.06.016.
[12] Moon B, Kim S, Park YH, et al. Depressive Symptoms are Associated with Progression to Dementia in Patients with Amyloid-Positive Mild Cognitive Impairment. J Alzheimers Dis 2017;58(4):1255–64. https://doi.org/10.3233/JAD-170225.
[13] Devanand DP, Lee S, Huey ED, Goldberg TE. Associations Between Neuropsychiatric Symptoms and Neuropathological Diagnoses of Alzheimer Disease and Related Dementias. JAMA Psychiatry 2022;79(4):359–67. https://doi.org/10.1001/JAMAPSYCHIATRY.2021.4363.
[14] Chen Y, Dang M, Zhang Z. Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: a systematic review of symptom-general and –specific lesion patterns. Mol Neurodegener 2021;16(1):1–22. https://doi.org/10.1186/S13024-021-00456-1. 2021 161.
[15] Zeng Q, Wang Y, Wang S, et al. Cerebrospinal fluid amyloid-β and cerebral microbleed are associated with distinct neuropsychiatric sub-syndromes in cognitively impaired patients. Alzheimers Res Ther 2024;16(1). https://doi.org/10.1186/S13195-024-01434-7.
[16] Donovan NJ, Locascio JJ, Marshall GA, et al. Longitudinal Association of Amyloid Beta and Anxious-Depressive Symptoms in Cognitively Normal Older Adults. Am J Psychiatry 2018;175(6):530–7. https://doi.org/10.1176/APPI.AJP.2017.17040442.
[17] Gatchel JR, Donovan NJ, Locascio JJ, et al. Depressive Symptoms and Tau Accumulation in the Inferior Temporal Lobe and Entorhinal Cortex in Cognitively Normal Older Adults: a Pilot Study. J Alzheimers Dis 2017;59(3):975–85. https://doi.org/10.3233/JAD-170001.
[18] Tissot C, Therriault J, Pascoal TA, et al. Association between regional tau pathology and neuropsychiatric symptoms in aging and dementia due to Alzheimer's disease. Alzheimer's Dement Transl Res Clin Interv 2021;7(1). https://doi.org/10.1002/TRC2.12154.
[19] Pink A, Krell-Roesch J, Syrjanen JA, et al. Interactions Between Neuropsychiatric Symptoms and Alzheimer's Disease Neuroimaging Biomarkers in Predicting Longitudinal Cognitive Decline. Psychiatr Res Clin Pract 2023;5(1):4–15. https://doi.org/10.1176/APPI.PRCP.20220036/ASSET/IMAGES/MEDIUM/RCP21057-FIG-0003.PNG.
[20] Sharif SF, Guan DX, Bodnar T, et al. Neuropsychiatric symptoms and progression to pathologically confirmed Alzheimer's disease. Brain. Published online April 2025;25. https://doi.org/10.1093/BRAIN/AWAF156.
[21] Buckley RF, Scott MR, Jacobs HIL, et al. Sex Mediates Relationships Between Regional Tau Pathology and Cognitive Decline. Ann Neurol 2020;88(5):921–32. https://doi.org/10.1002/ANA.25878.

[22] Therriault J, Benedet AL, Pascoal TA, et al. APOEε4 potentiates the relationship between amyloid-β and tau pathologies. Mol Psychiatry 2021;26(10):5977–88. https://doi.org/10.1038/S41380-020-0688-6.
[23] Arenaza-Urquijo EM, Przybelski SA, MacHulda MM, et al. Better stress coping associated with lower tau in amyloid-positive cognitively unimpaired older adults. Neurology 2020;94(15):e1571–9. https://doi.org/10.1212/WNL.0000000000008979.
[24] Shcherbinin S, Morris A, Higgins IA, et al. Tau as a diagnostic instrument in clinical trials to predict amyloid in Alzheimer's disease. Alzheimer's Dement (New York, N Y) 2023;9(3). https://doi.org/10.1002/TRC2.12415.
[25] Baker LD, Snyder HM, Espeland MA, et al. Study design and methods: U.S. study to protect brain health through lifestyle intervention to reduce risk (U.S. POINTER). Alzheimers Dement 2024;20(2):769–82. https://doi.org/10.1002/alz.13365.
[26] Florian H, Wang D, Arnold SE, et al. Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. Brain 2023;146(6):2275–84. https://doi.org/10.1093/brain/awad024.
[27] Baker SL, Lockhart SN, Price JC, et al. Reference Tissue-Based Kinetic Evaluation of 18F-AV-1451 for Tau Imaging. J Nucl Med 2017;58(2):332–8. https://doi.org/10.2967/jnumed.116.175273.
[28] Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [18F]-AV-1451 tau PET data. Data Br 2017;15:648–57. https://doi.org/10.1016/J.DIB.2017.10.024.
[29] Landau SM, Breault C, Joshi AD, et al. Amyloid-β imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med 2013;54(1):70–7. https://doi.org/10.2967/jnumed.112.109009.
[30] Landau SM, Fero A, Baker SL, et al. Measurement of Longitudinal β-Amyloid Change with 18F-Florbetapir PET and Standardized Uptake Value Ratios. J Nucl Med 2015;56(4):567–74. https://doi.org/10.2967/JNUMED.114.148981.
[31] Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 2015;11(1):1–15. https://doi.org/10.1016/J.JALZ.2014.07.003. e4.
[32] Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimer's Res Ther 2021;13(1):1–10. https://doi.org/10.1186/S13195-021-00836-1. 2021 131.
[33] Cummings J. The Neuropsychiatric Inventory: development and Applications. J Geriatr Psychiatry Neurol 2020;33(2):73–84. https://doi.org/10.1177/0891988719882102.
[34] Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 1997;48(5 SUPPL. 6). https://doi.org/10.1212/WNL.48.5_SUPPL_6.10S.
[35] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44(12):2308–14. https://doi.org/10.1212/WNL.44.12.2308.
[36] Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, et al. Depression as a Risk Factor for Alzheimer's Disease: a Systematic Review of Longitudinal Meta-Analyses. J Clin Med 2021;10(9):1809. https://doi.org/10.3390/JCM10091809.
[37] Pietrzak RH, Lim YY, Neumeister A, et al. Amyloid-β, anxiety, and cognitive decline in preclinical alzheimer disease a multicenter, prospective cohort study. JAMA Psychiatry 2015;72(3):284–91. https://doi.org/10.1001/jamapsychiatry.2014.2476.
[38] Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt 2014;34(5):502–8. https://doi.org/10.1111/OPO.12131.
[39] Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63(5):530–8. https://doi.org/10.1001/ARCHPSYC.63.5.530.
[40] Ossenkoppele R, Schonhaut DR, Schöll M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139(5):1551–67. https://doi.org/10.1093/BRAIN/AWW027.
[41] Ehrenberg AJ, Suemoto CK, França Resende E, de P, et al. Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. J Alzheimers Dis 2018;66(1):115–26. https://doi.org/10.3233/JAD-180688.
[42] Krell-Roesch J, Vassilaki M, Mielke MM, et al. Cortical β-amyloid burden, neuropsychiatric symptoms, and cognitive status: the Mayo Clinic Study of Aging. Transl Psychiatry 2019;9(1). https://doi.org/10.1038/s41398-019-0456-z.
[43] Macedo AC, Therriault J, Tissot C, et al. Modeling the progression of neuropsychiatric symptoms in Alzheimer's disease with PET-based Braak staging. Neurobiol Aging 2024;144:127–37. https://doi.org/10.1016/J.NEUROBIOLAGING.2024.09.009.
[44] Kaufman SK, Del Tredici K, Thomas TL, Braak H, Diamond MI. Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. Acta Neuropathol 2018;136(1):57–67. https://doi.org/10.1007/S00401-018-1855-6.
[45] Heneka MT, Carson MJ, El KJ, et al. Neuroinflammation in Alzheimer's Disease. Lancet Neurol 2015;14(4):388–405. https://doi.org/10.1016/S1474-4422(15)70016-5.
[46] Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 2014;128(6):755–66. https://doi.org/10.1007/S00401-014-1349-0.
[47] Adams JN, Maass A, Harrison TM, Baker SL, Jagust WJ. Cortical tau deposition follows patterns of entorhinal functional connectivity in aging. Elife 2019;8. https://doi.org/10.7554/ELIFE.49132.
[48] Johansson M, Stomrud E, Lindberg O, et al. Apathy and anxiety are early markers of Alzheimer's disease. Neurobiol Aging 2020;85:74–82. https://doi.org/10.1016/j.neurobiolaging.2019.10.008.
[49] Babulal GM, Chen L, Doherty JM, Murphy SA, Johnson AM, Roe CM. Longitudinal Changes in Anger, Anxiety, and Fatigue Are Associated with Cerebrospinal Fluid Biomarkers of Alzheimer's Disease. J Alzheimers Dis 2022;87(1):141–8. https://doi.org/10.3233/JAD-215708.
[50] Demnitz-King H, Saba L, Lau Y, et al. Association between anxiety symptoms and Alzheimer's disease biomarkers in cognitively healthy adults: a systematic review and meta-analysis. J Psychosom Res 2023;166:111159. https://doi.org/10.1016/J.JPSYCHORES.2023.111159.
[51] Gonzales MM, Samra J, O'Donnell A, et al. Association of Midlife Depressive Symptoms with Regional Amyloid-β and Tau in the Framingham Heart Study. J Alzheimers Dis 2021;82(1):249–60. https://doi.org/10.3233/JAD-210232.
[52] De Vito AN, et al. Parallel changes in cognition, neuropsychiatric symptoms, and amyloid in cognitively unimpaired older adults and those with mild cognitive impairment. Alzheimer's & dementia: the journal of the Alzheimer's Association 2025;21(2):e14568. https://doi.org/10.1002/alz.14568.
[53] Kim H, Levine A, Cohen D, et al. The Role of Amyloid, Tau, and APOE Genotype on the Relationship Between Informant-Reported Sleep Disturbance and Alzheimer's Disease Risks. J Alzheimers Dis 2022;87(4):1567–80. https://doi.org/10.3233/JAD-215417.
[54] Lucey BP. It's complicated: the relationship between sleep and Alzheimer's disease in humans. Neurobiol Dis 2020;144:105031. https://doi.org/10.1016/J.NBD.2020.105031.
[55] Buckley RF, Mormino EC, Rabin JS, et al. Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured by Positron Emission Tomography in Clinically Normal Older Adults. JAMA Neurol 2019;76(5):542–51. https://doi.org/10.1001/JAMANEUROL.2018.4693.
[56] Pereira JB, Harrison TM, La Joie R, Baker SL, Jagust WJ. Spatial patterns of tau deposition are associated with amyloid, ApoE, sex, and cognitive decline in older adults. Eur J Nucl Med Mol Imaging 2020;47(9):2155–64. https://doi.org/10.1007/S00259-019-04669-X.
[57] Wang Y-T, Therriault J, Servaes S, et al. Sex-specific modulation of amyloid-β on tau phosphorylation underlies faster tangle accumulation in females. Brain 2024;147(4):1497–510. https://doi.org/10.1093/BRAIN/AWAD397.
[58] Sundermann EE, Panizzon MS, Chen X, Andrews M, Galasko D, Banks SJ. Sex differences in Alzheimer's-related Tau biomarkers and a mediating effect of testosterone. Biol Sex Differ 2020;11(1). https://doi.org/10.1186/S13293-020-00310-X.
[59] Pichet Binette A, Vachon-Presseau É, Morris JC, et al. Amyloid and Tau Pathology Associations With Personality Traits, Neuropsychiatric Symptoms, and Cognitive Lifestyle in the Preclinical Phases of Sporadic and Autosomal Dominant Alzheimer's Disease. Biol Psychiatry 2021;89(8):776–85. https://doi.org/10.1016/j.biopsych.2020.01.023.
[60] Cai Y, Fang L, Li A, et al. Educational attainment, Aβ, tau, and structural brain reserve in Alzheimer's disease. Alzheimer's Dement 2025;21(2):e14400. https://doi.org/10.1002/ALZ.14400.
[61] Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord 2006;20(2):112–7. https://doi.org/10.1097/01.wad.0000213815.20177.19.
[62] Lai CKY. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. Clin Interv Aging 2014;9:1051–61. https://doi.org/10.2147/CIA.S63504.
[63] Trzepacz PT, Saykin A, Yu P, et al. Subscale Validation of the Neuropsychiatric Inventory Questionnaire (NPI-Q): comparison of ADNI and NACC Cohorts. Am J Geriatr Psychiatry 2013;21(7):607–22. https://doi.org/10.1016/J.JAGP.2012.10.027.