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RESEARCH ARTICLE

Association of item-level responses to cognitive function index with tau pathology and hippocampal volume in the A4 Study

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Abstract

INTRODUCTION: Alzheimer's disease (AD) has a long preclinical phase in which individuals may accumulate amyloid beta (Aβ) and tau pathology without noticeable cognitive impairment. Subjective cognitive impairment reports can provide early insights into cognitive decline.

METHODS: In the A4 Study, 339 cognitively unimpaired, Aβ-positive individuals underwent tau positron emission tomography imaging. Tau status was classified based on medial temporal lobe tau standardized uptake value ratios (tau_{MTL}). Participants and study partners assessed cognitive changes using the 15-item Cognitive Function Index (CFI) questionnaire. We explored the relationship among tau_{MTL}, hippocampal volume (HVa), and CFI reports.

RESULTS: Higher tau_{MTL} was associated with participant-reported concerns about memory and navigation, and with study partner–reported difficulty remembering appointments. Lower HVa showed a marginal association with participant-reported driving difficulty.

DISCUSSION: These findings support the utility of participant- and study partner–reported concerns as early indicators of preclinical AD pathology, with potential value for early detection and trial enrichment strategies.

KEYWORDS
hippocampal volume, preclinical Alzheimer's disease, subjective cognitive decline, tau positron emission tomography imaging

Highlights

- Higher tau in the medial temporal lobe (tau_{MTL}) was linked to participant-reported memory and orientation decline such as needing reminders or getting lost.
- Higher tau_{MTL} was associated with increased memory-related concerns, such as needing help with appointments and asking repetitive questions.
- Lower hippocampal volume was associated with spatial memory and navigation such as driving difficulties and greater memory decline as reported by study partners.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a long preclinical phase, during which individuals may appear cognitively normal while the pathological hallmarks of the disease, including amyloid beta (Aβ) plaques and tau tangles, are already developing in the brain.[1] As clinical trials increasingly target this early disease stage, identifying subtle cognitive changes before objective impairment is crucial for tracking disease progression and evaluating the efficacy of potential interventions.[2] Identifying these early shifts is crucial for accurately quantifying disease progression and the effectiveness of potential therapeutic interventions.[3]

Subjective cognitive decline (SCD)—defined as the perception of cognitive decline despite intact performance on standardized cognitive tests—may offer multiple clinical and research benefits.[4] First, SCD may serve as an early signal of neurodegenerative changes that are not yet captured by objective testing. Second, subjective reports can provide insight into the lived experience of cognitive decline, highlighting concerns that may be overlooked by traditional assessments. Third, SCD is associated with increased risk of developing mild cognitive impairment (MCI) or dementia, underscoring its prognostic value.[5] Fourth, SCD measures offer a practical and scalable approach to tracking early symptoms and identifying individuals at risk for AD. Finally, incorporating subjective perspectives from both participants and study partners may enhance detection of subtle functional decline and inform clinical decision making.

Despite these potential benefits, limited work has examined how specific subjective concerns—rather than overall scores—map onto AD biomarkers in preclinical populations. Prior studies have largely focused on total Cognitive Function Index (CFI) or SCD scores, treating these measures as unidimensional constructs. However, subjective concerns span a range of cognitive and functional domains, and certain items may be more sensitive to early AD-related changes than others. Additionally, the relative value of participant versus study partner perspectives remains unclear, particularly in asymptomatic, Aβ+ individuals who are still functionally independent.

The CFI is a validated tool developed to assess subjective cognitive concerns in both research and clinical settings.[6] Prior studies have demonstrated associations between composite CFI scores and both cognitive performance and Aβ deposition.[7,8] For example, Robinson et al. reported that associations between CFI scores and biomarkers varied by race/ethnicity, but that self- and study partner reports were generally consistent across groups.[9] Amariglio et al. found that both participant and study partner CFI scores predicted future cognitive decline in cognitively normal older adults, with self-reports appearing particularly sensitive to early changes.[10] A subsequent analysis identified subjective cognitive changes reported by participants and study partners in Aβ+ individuals. Their findings indicated that participants were more likely than study partners to report changes on most CFI items; however, specific CFI items were associated with elevated Aβ levels in both groups, highlighting the importance of considering both sources of information in clinical trials.[11] More recently, Jadick et al. examined associations between tau positron emission tomography (PET), Aβ, and subjective cognitive concerns using pooled data from three cohorts including the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study.[12] Their results showed that both participant and study partner CFI scores were associated with regional tau burden, reinforcing the potential utility of subjective reports in preclinical AD detection.

In this study, we investigated cross-sectional associations between SCD, as measured by CFI, and AD biomarkers—specifically tau pathology and adjusted hippocampal volume (HVa)—in cognitively unimpaired, Aβ+ participants from the A4 Study. While prior research has established links between SCD and amyloid burden, the relationship between SCD and tau pathology in cognitively normal individuals remains less well characterized for Aβ+ participants, despite mounting evidence that tau pathology plays a central role in AD-related cognitive impairment and demonstrates stronger correlations with both subjective complaints and objective cognitive decline than Aβ. Importantly, prior research has primarily focused on composite SCD scores (i.e., total CFI score), but SCD represents a broad range of perceived impairment, and only a subset may be particularly sensitive to early AD pathology. Our study addresses this gap by leveraging item-level analyses to explore the heterogeneity of subjective cognitive complaints and their associations with two key AD biomarkers—tau in the medial temporal lobe (tau_{MTL}) and HVa. We also examine both participant- and

RESEARCH IN CONTEXT

1. **Systematic review**: Previous studies have shown that Alzheimer's disease (AD) has a prolonged preclinical phase characterized by the accumulation of amyloid beta (Aβ) and tau pathologies, often without overt cognitive impairment. Subjective cognitive impairment (SCI) reports from individuals and study partners have been explored as early indicators of cognitive decline. However, the relationship between these subjective reports and underlying neurodegenerative changes, such as tau deposition and hippocampal atrophy, has not been consistently examined in asymptomatic Aβ-positive individuals.
2. **Interpretation**: This study shows that early SCI, as reported by both participants and study partners, is associated with higher tau in the medial temporal lobe (tau_{MTL}) and lower hippocampal volume in Aβ-positive individuals. These findings suggest that SCI reports can serve as early markers of neurodegeneration.
3. **Future directions**: Future research should focus on longitudinal studies to track how subjective cognitive changes evolve over time and whether they predict progression to clinical AD. Expanding the use of multimodal biomarkers in diverse populations could help refine early diagnostic criteria and identify individuals at higher risk for cognitive decline.

study partner–reported items to clarify the unique and complementary contributions of these perspectives in the early detection of AD.

2 | METHODS

2.1 | Participants

Data were obtained from the A4 Study, a multi-site clinical trial conducted across 67 locations in the United States, Australia, Japan, and Canada. All participants provided written informed consent, and institutional review board approval was obtained at each site. The study was coordinated by the Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California, and de-identified data were made available through the Laboratory for Neuro Imaging.[13]

A total of 6763 cognitively unimpaired individuals aged 65 to 85 were screened for inclusion in the A4 Study. Individuals who underwent screening for the A4 Study were determined to be cognitively unimpaired, meeting criteria including a global Clinical Dementia Rating (CDR) score of 0, Mini-Mental State Examination (MMSE) score between 25 and 30, and a Logical Memory II subscale delayed paragraph recall (LM-IIa) score on the Wechsler Memory Scale-Revised (WMS-R) ranging from 6 to 18.[14] Eligibility for A4 was contingent on elevated amyloid burden as determined by florbetapir PET. Those who met all other criteria but exhibited lower amyloid levels were enrolled in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN study, forming a separate cohort for the further investigation of their cognitive, clinical, and biological changes. Of those screened, 4486 underwent Aβ PET imaging, and a subset received tau PET.[15,16] In a subgroup of participants, ^{18}F-flortaucipir tau PET imaging was conducted. For this analysis, we included 339 Aβ+ individuals who also had tau PET data and valid CFI reports (see Figure S1 in supporting information for flowchart).

2.2 | CFI

The CFI was used to assess subjective cognitive concerns through both participant and study partner reports. Scores were standardized to account for missing or non-applicable responses, and higher scores reflect greater cognitive concern.[6,10,17] See Supplementary Methods in supporting information for more details about CFI and computational details.

2.3 | Amyloid PET imaging and determination of Aβ status

Amyloid PET imaging with ^{18}F-florbetapir was used to classify participants as Aβ+ or Aβ– based on a combined standardized uptake volume ratio (SUVR) and visual read approach. A SUVR < 1.15 indicated a non-elevated amyloid level.[11] See Supplementary Methods for imaging protocols and classification details.

2.4 | Tau PET imaging and determination of tau status

Tau PET imaging was performed using 18F-flortaucipir, with SUVRs calculated for a medial temporal lobe (MTL) region of interest (ROI). Tau positivity was defined using a cutoff derived from Aβ– participants.[18–21] Full methodological details are provided in Supplementary Methods.

2.5 | Volumetric magnetic resonance imaging

High-resolution magnetic resonance imaging (MRI) scans were analyzed using FreeSurfer 6.0 and NeuroQuant to extract HVa, adjusted for intracranial volume. HVa served as a marker of neurodegeneration. See Supplementary Methods for segmentation and adjustment procedures.[13]

2.6 | Genetic measures

Apolipoprotein E (*APOE*) ε4 allele status (0, 1, or 2 alleles) was included as a categorical variable to account for genetic risk of AD.[22] Further details are provided in Supplementary Methods.

2.7 | Statistical analyses

Demographic information from participants and study partners were summarized for the entire sample. Continuous data were described using mean and standard deviations (SDs) and group differences were assessed using independent sample *t* tests. For categorical data, analyses were conducted using the chi-squared test and the Fisher exact test. Pearson correlation coefficients were used to evaluate the relationships among Aβ, tau_{MTL}, and HVa. Multiple linear regression was used to assess the relationships among the total CFI scores (reported by participants or study partners), pathological tau levels (measured by PET imaging), and HVa (as a marker of neurodegeneration), adjusting for demographic variables.

We examined associations between CFI item endorsement (dichotomized as 0 = no endorsement vs. 1 = yes or maybe) and AD-related imaging biomarkers using three logistic regression models.[23] All models were adjusted for key demographic and genetic covariates: *APOE* ε4 carrier status, age, sex, and education.

1. **Model 1** included Aβ and tau SUVR in the medial temporal lobe (tau_{MTL}) as continuous predictors.
2. **Model 2** included Aβ and HVa.
3. **Model 3** included tau MTL and HVa to evaluate their independent effects in combination.

TABLE 1 Amyloid positive participants stratified for tau MTL.

Variable	TOTAL	T−	T+	
N	339	259	80	*p* value
Age (years), mean (SD)	72.38 (4.87)	72.16 (4.75)	73.10 (5.22)	0.132
Female	197 (58.1%)	144 (55.6%)	53 (66.2%)	0.091
Race				0.936[a]
White	310 (91.4%)	237 (91.5%)	73 (91.2%)	
Black	9 (2.7%)	7 (2.7%)	2 (2.5%)	
Others	20 (5.9%)	15 (5.8%)	5 (6.2%)	
Education (years), mean (SD)	16.15 (2.85)	16.12 (2.91)	16.262(2.68)	0.688
Marital status				0.402[a]
Married	243 (71.7%)	188 (72.6%)	55 (68.8%)	
Widowed	36 (10.6%)	30 (11.6%)	6 (7.5%)	
Divorced	44 (13.0%)	30 (11.6%)	14 (17.5%)	
Never married	11 (3.2%)	7 (2.7%)	4 (5.0%)	
Unknown/other	5 (1.5%)	4 (1.5%)	1 (1.2%)	
Amyloid (Aβ)	1.35 (0.16)	1.33 (0.15)	1.43 (0.19)	< 0.001
tau_{MTL}	1.23 (0.16)	1.16 (0.08)	1.46 (0.14)	**< 0.001**
Hippocampal (cm^3)	6.75 (0.80)	6.82 (0.79)	6.52 (0.80)	**0.003**
APOE ε4 +	207 (61.1%)	145 (56.0%)	62 (77.5%)	< 0.001
CFI participants—mean (SD)	0.16 (0.14)	0.14 (0.13)	0.21 (0.17)	< 0.001
CFI study partner—mean (SD)	0.11 (0.14)	0.10 (0.13)	0.13 (0.16)	0.107
Participant retired				0.414[a]
Yes	268 (79.1%)	205 (79.2%)	63 (78.8%)	
No	65 (19.2%)	48 (18.5%)	17 (21.2%)	
Not applicable	6 (1.8%)	6 (2.3%)	0 (0.0%)	
SP sex—female	204 (60.2%)	157 (60.6%)	47 (58.8%)	0.765
Living with participant	227 (67.0%)	172 (66.4%)	5 (68.8%)	0.697
PACC	−0.63 (2.76)	−0.31 (2.69)	−1.66 (2.73)	< 0.001
DLM	11.38 (3.41)	11.71 (3.40)	10.29 (3.24)	< 0.001
MMSE	28.61 (1.29)	28.67 (1.29)	28.40 (1.28)	0.105
DSS	42.15 (9.51)	42.60 (9.49)	40.71 (9.49)	0.121
FCSRT96	75.29 (6.25)	75.95 (5.92)	73.14 (6.81)	**< 0.001**

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CFI, Cognitive Function Index; DLM, Delayed Logical Memory (range, 0–25); DSS, Digit Symbol Substitution (max score, 91); FCSRT, Free and Cued Selective Reminding Test (range, 0–96); MMSE, Mini-Mental State Examination (range, 0–30); MTL, medial temporal lobe; N-Miss, number of missing; P, participants; PACC, Preclinical Alzheimer Cognitive Composite; SD, standard deviation; SP, study partner; tau_{MTL}, tau standardized uptake value ratios in medial temporal lobe.
[a]Fisher exact test.

Each model was run separately for participant-reported and study partner–reported CFI items. Given the large number of comparisons across 15 items (for both informants), we applied the Benjamini–Hochberg procedure to control the false discovery rate (FDR).[24] These steps ensure that our findings are interpreted in the appropriate statistical context, especially given the moderate sample size. Additionally, we computed the Cohen kappa for each item to assess agreement between participant and study partner reports and used the McNemar test to examine concordance patterns. All analyses were performed using R version 4.3.1.

3 | RESULTS

3.1 | Demographics

A total of 339 Aβ+ individuals with tau PET imaging were eligible for this analysis. Among these participants, 23.6% were classified as tau positive in the medial temporal lobe (T+), and 58.1% were female. The T+ group had a higher rate of *APOE* ε4 alleles compared to the T− group. No significant differences were observed between the T+ and T− groups in terms of sex, education background, marital status, or retirement status (Table 1).

TABLE 2 Linear regression results for associations between total Cognitive Function Index (CFI) scores (participant and study partner reported) and demographic/imaging biomarkers from Aβ+ participants.

	Participants reported CFI score			Study partner reported CFI score		
Outcome	Estimate	Std. Error	Pr(> |t|)	Estimate	Std. Error	Pr(> |t|)
(Intercept)	0.005	0.115	0.965	0.140	0.113	0.216
APOE+	0.077	0.116	0.511	0.023	0.114	0.839
Female	−0.089	0.124	0.473	−0.266	0.122	**0.030**
Age	0.062	0.063	0.33	−0.026	0.062	0.677
Education	−0.024	0.055	0.661	0.079	0.054	0.143
Amyloid (Aβ)	0.123	0.058	**0.036**	0.148	0.057	**0.011**
HVa	−0.025	0.069	0.717	−0.076	0.068	0.264
tau_{MTL}	0.144	0.058	**0.013**	0.111	0.057	0.051

Abbreviation: Aβ, amyloid beta; *APOE*, apolipoprotein E; HVa: adjusted hippocampal volume; tau_{MTL}, tau standardized uptake value ratios in medial temporal lobe.

Statistical analysis revealed a significant difference in Aβ levels between the T+ and T− groups ($P < 0.001$). The T+ group demonstrated significantly higher mean Aβ values (mean = 1.43, SD = 0.19) compared to the T− group (mean = 1.33, SD = 0.15). We also found a significant reduction in adjusted HVa in the T+ group (6.52, SD = 0.80, $p = 0.003$; Table 1).

Compared to the T+ group, the T− group had higher cognitive performance across several objective cognitive measures, including the Preclinical Alzheimer Cognitive Composite (PACC), logical memory–delayed recall (DLM), and Free and Cued Selective Reminding Test (FCSRT96), all showing significant differences with p values of < 0.001. The total CFI scores for participants were significantly higher in the T+ group ($p < 0.001$). However, the total CFI score reported by study partner did not differ significantly between groups ($p = 0.141$; Table 1).

3.2 | Total CFI score analyses

Pearson correlations revealed a modest inverse association between HVa and tau_{MTL} ($r = -0.168$, $p = 0.002$), as well as between HVa and Aβ ($r = -0.230$, P$p < 0.001$). Aβ and tau_{MTL} were moderately positively correlated ($r = 0.313$, $p < 0.001$). In regression models examining participant-reported total CFI scores, higher tau_{MTL} was significantly associated with greater subjective cognitive concerns ($\beta = 0.15$, $p = 0.011$). HVa was not significantly associated with participant CFI scores. For study partner–reported total CFI, tau_{MTL} showed a non-significant positive trend ($\beta = 0.11$, $p = 0.064$). While participants were limited to Aβ+ individuals, Aβ was significantly associated with higher CFI scores in both models (participant: $\beta = 0.12$, $p = 0.037$; study partner: $\beta = 0.15$, $p = 0.008$; Table 2).

To extend our primary findings, we conducted supplementary analyses that included models using neocortical tau (tau_{NEO}) in the Aβ+ cohort, as well as models incorporating both tau_{NEO} and tauMTL in the combined A4 + LEARN cohort. These results are presented in Tables S1 through S4 in supporting information.

3.3 | Concordance between participant and study partner reports on CFI items

The most frequently endorsed items by participants included "difficulty remembering things" (63%), "depending on written notes" (46%), and "misplacing things" (32%). These same items were endorsed less frequently by study partners (28%, 29%, and 24%, respectively). The least endorsed items across both groups included difficulties with appliances, financial tasks, and hobbies (Figure 1).

Additionally, to quantify the concordance between participant and study partner reports, we calculated the Cohen kappa for each question. The higher values of Cohen kappa indicating stronger agreement between participant and study partner. Cohen kappa values varied across items, with the highest agreement observed for "seen a doctor for memory concerns" and "decline in work performance," while the lowest agreement was seen for "struggling with hobbies" and "noticeable memory decline" (Figure S2 in supporting information). McNemar tests revealed significant discrepancies in endorsement patterns for several items.

3.4 | Item-level analysis

We examined associations between participant-reported CFI item endorsement and AD biomarkers using three logistic regression models (Table 3).

Model 1 explored the association between tau_{MTL} and self-reported CFI item endorsement. In the participant analysis, tau_{MTL} emerged as a significant independent predictor for several items, including "seen a doctor for memory concerns" (odds ratio [OR] = 1.743, FDR $p = 0.007$) and "feeling lost while navigating" (OR = 1.550, FDR $p = 0.012$). For "depending on written notes" (OR = 1.370, FDR $p = 0.075$) and "decline in work performance" (OR = 1.449, FDR $p = 0.160$), tau_{MTL} just showed a trend toward significance. Aβ also showed a significant independent effect for "seen a doctor for memory concerns" (OR = 1.574, $p = 0.028$),

FIGURE 1 Item-level endorsement proportion for Cognitive Function Index (CFI) items, comparing participant self-reports (P) and study partner reports (SP). Categories marked "N/A" indicate non-applicable responses.

and a trend toward significance for "less interest in social events" (OR = 1.426, Pp = 0.090).

Model 2 examined the association between HVa and item-level CFI endorsement. None of the specific CFI items demonstrated significant associations with HVa. However, lower HVa showed a trend toward significance for the driving difficulty item (OR = 0.670, FDR p = 0.100), though it did not survive correction for multiple comparison.

In Model 3, the combined influence of tau_{MTL} and HVa on CFI items was evaluated (Figure 2). The findings remained consistent with those from Model 1. Specifically, participants endorsed CFI items such as having "seen a doctor for memory concerns" (OR = 1.692, p = 0.017), and "feeling lost while navigating" (OR = 1.555, p = 0.016) with tau_{MTL} showing significant effects. Similar to Model 1, for the item "depending on written notes" (OR = 1.385, FDR p = 0.073), tau_{MTL} approached but did not reach significance after FDR adjustment. On the other hand, HVa approached significance for the item for "challenges in driving" (OR = 0.676, P = 0.137) but did not demonstrate significant associations with any CFI items after FDR adjustment.

Next, we repeated the analysis for study partner–reported CFI items (Table 4). Model 1 explored the association between tau_{MTL} and item endorsement. Higher tau_{MTL} was significantly associated with increased endorsement of one item: "needing help recalling appointments" (OR = 1.589, p = 0.005). No other items reached statistical significance in this model. Model 2 examined the association between HVa and study partner–reported item endorsement. Smaller HVa was associated with increased endorsement of the item "noticeable memory decline," though this association did not reach statistical significance after adjustment (OR = 0.660, FDR p = 0.085). In Model 3, which included both tau_{MTL} and HVa as predictors, tau_{MTL} remained significantly associated with endorsement of "needing help recalling appointments" (OR = 1.600, p = 0.002). In addition, endorsement of "asking the same question repeatedly" showed a trend toward association with higher tau_{MTL}, though it did not reach significance after FDR adjustment (OR = 1.363, p = 0.090). No study partner–reported items were significantly associated with HVa in this model.

In addition to our primary analyses restricted to Aβ+ participants, we conducted supplementary analyses to provide broader context and assess the generalizability of findings. These include models using tau burden in the neocortex (tau_{NEO}) and models incorporating the full A4 + LEARN sample (n = 440).

Our primary analyses focused on tau_{MTL} because of its early involvement in preclinical AD and its greater relevance in cognitively unimpaired Aβ+ individuals. However, the supplementary analyses—including alternative tau regions and broader samples—provide additional insights and are detailed in Tables S5 through S8 in supporting information.

4 | DISCUSSION

In a sample of cognitively unimpaired, Aβ+ individuals, we investigated the association of total and item-level CFI scores with tau pathology, measured by the regional tau composite score of the MTL, and neurodegeneration, measured by HVa. Our results indicate that higher tau_{MTL} levels and higher Aβ levels, at elevated Aβ, were both associated with higher total CFI scores as reported by participants. The

TABLE 3 Comparison of logistic models from the Aβ+ cohort for participant Cognitive Function Index (CFI) items.

	Model 1		Model 2		Model 3	
	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value
Written						
Aβ	0.818 (0.643, 1.035)	0.223	0.894 (0.710, 1.123)	0.931	0.824 (0.647, 1.045)	0.299
tau_{MTL}	1.370 (1.081, 1.756)	0.075			1.385 (1.089, 1.780)	0.073
HVa			1.030 (0.781, 1.360)	0.931	1.091 (0.822, 1.450)	0.732
Social						
Aβ	1.426 (1.039, 1.947)	0.090	**1.49 (1.093, 2.024)**	**0.038**	1.451 (1.055, 1.987)	0.082
tau_{MTL}	1.111 (0.793, 1.527)	0.615			1.139 (0.807, 1.579)	0.546
HVa			1.154 (0.766, 1.741)	0.562	1.185 (0.783, 1.793)	0.546
Repeat						
Aβ	1.154 (0.821, 1.593)	0.460	1.175 (0.843, 1.612)	0.512	1.140 (0.809, 1.578)	0.546
tau_{MTL}	1.169 (0.841, 1.595)	0.460			1.144 (0.820, 1.573)	0.546
HVa			0.849 (0.56, 1.280)	0.512	0.879 (0.576, 1.332)	0.546
Active						
Aβ	1.444 (0.960, 2.136)	0.242	1.443 (0.972, 2.11)	0.215	1.451 (0.960, 2.157)	0.276
tau_{MTL}	0.976 (0.619, 1.479)	0.912			0.980 (0.619, 1.494)	0.927
HVa			1.044 (0.609, 1.785)	0.874	1.041 (0.603, 1.786)	0.927
Concern						
Aβ	1.574 (1.082, 2.285)	**0.028**	**1.734 (1.213, 2.496)**	**0.009**	**1.546 (1.059, 2.252)**	**0.044**
tau_{MTL}	1.743 (1.226, 2.494)	**0.007**			**1.692 (1.179, 2.443)**	**0.017**
HVa			0.699 (0.412, 1.171)	0.247	0.833 (0.490, 1.404)	0.566
Recall						
Aβ	1.138 (0.879, 1.492)	0.391	1.063 (0.826, 1.381)	0.755	1.126 (0.868, 1.478)	0.508
tau_{MTL}	0.799 (0.622, 1.026)	0.182			0.786 (0.609, 1.013)	0.252
HVa			0.932 (0.687, 1.262)	0.755	0.889 (0.653, 1.209)	0.516
Appliance						
Aβ	1.271 (0.779, 2.025)	0.448	1.274 (0.790, 2.006)	0.424	1.269 (0.773, 2.032)	0.526
tau_{MTL}	1.016 (0.590, 1.674)	0.992			1.014 (0.588, 1.681)	0.994
HVa			0.985 (0.531, 1.804)	0.988	0.987 (0.529, 1.813)	0.994
Follow						
Aβ	1.309 (0.961, 1.772)	0.205	1.419 (1.052, 1.908)	0.071	1.331 (0.973, 1.809)	0.207
tau_{MTL}	1.269 (0.939, 1.700)	0.205			1.291 (0.951, 1.742)	0.207
HVa			1.078 (0.726, 1.602)	0.929	1.138 (0.764, 1.697)	0.689
Lost						
Aβ	1.086 (0.780, 1.488)	0.721	1.216 (0.889, 1.645)	0.393	1.088 (0.778, 1.498)	0.819
tau_{MTL}	1.550 (1.153, 2.085)	**0.012**			**1.555 (1.150, 2.106)**	**0.016**
HVa			0.916 (0.614, 1.361)	0.896	1.018 (0.680, 1.521)	0.930
Help						
Aβ	1.359 (0.998, 1.844)	0.079	1.450 (1.073, 1.954)	**0.034**	1.368 (1.001, 1.861)	0.088
tau_{MTL}	1.337 (0.987, 1.797)	0.079			1.349 (0.990, 1.828)	0.088
HVa			0.981 (0.663, 1.450)	0.925	1.058 (0.711, 1.570)	0.836

(Continues)

TABLE 3 (Continued)

	Model 1		Model 2		Model 3	
	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value
Memory						
Aβ	1.008 (0.779, 1.297)	0.949	1.069 (0.833, 1.365)	0.790	1.006 (0.776, 1.297)	0.961
tau_{MTL}	1.278 (0.999, 1.638)	0.178			1.274 (0.994, 1.639)	0.225
HVa			0.938 (0.691, 1.270)	0.790	0.981 (0.721, 1.332)	0.961
Misplace						
Aβ	1.237 (0.971, 1.579)	0.198	1.299 (1.027, 1.649)	0.208	1.232 (0.966, 1.574)	0.249
tau_{MTL}	1.266 (0.999, 1.610)	0.179			1.259 (0.991, 1.606)	0.249
HVa			0.917 (0.686, 1.225)	0.738	0.957 (0.713, 1.283)	0.794
Money						
Aβ	1.367 (0.844, 2.167)	0.332	1.375 (0.858, 2.163)	0.303	1.340 (0.821, 2.138)	0.452
tau_{MTL}	1.149 (0.684, 1.848)	0.608			1.120 (0.665, 1.819)	0.656
HVa			0.825 (0.435, 1.531)	0.547	0.848 (0.443, 1.582)	0.656
Drive						
Aβ	1.043 (0.757, 1.413)	0.791	1.016 (0.743, 1.368)	0.967	1.006 (0.727, 1.369)	0.972
tau_{MTL}	1.097 (0.808, 1.468)	0.758			1.039 (0.762, 1.398)	0.972
HVa			0.670 (0.451, 0.982)	0.100	0.676 (0.452, 0.997)	0.137
Work						
Aβ	1.127 (0.734, 1.674)	0.765	1.207 (0.804, 1.765)	0.756	1.096 (0.709, 1.639)	0.910
tau_{MTL}	1.449 (1.003, 2.079)	0.160			1.403 (0.959, 2.030)	0.298
HVa			0.736 (0.433, 1.235)	0.756	0.812 (0.476, 1.368)	0.910

Note: All models were adjusted for *APOE* ε4 status, sex, age, and education. Model 1 included Aβ and tau SUVR in the MTL as continuous variables, Model 2 included Aβ and hippocampal volume as continuous variables, and Model 3 included Aβ and tau SUVR in the MTL as continuous variables.
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; FDR, false discovery rate; HVa, adjusted hippocampal volume; MTL, medial temporal lobe; SUVR, standardized uptake value ratio; tau_{MTL}, tau standardized uptake value ratios in medial temporal lobe.

association between tau_{MTL} and total CFI scores reported by study partners was weaker and not significant. When investigating item-level CFI scores with AD biomarkers, we found that greater tau_{MTL} levels were associated with few items on the self-reported CFI and only one non-identical item on the study partner–reported CFI. The association between adjusted HVa and item-level CFI responses was weak and marginally significant for one item on both the self-report and study partner versions.

Previous studies have shown that Aβ+ individuals report higher total CFI scores, both by self-report and study partners, compared to Aβ− individuals.[26] It has also been shown that different items on CFI as reported by participants and study partners were associated with higher amyloid burden in the A4 Study.[11] In the current study, which was limited to Aβ+ participants, higher levels of Aβ were associated with higher total CFI scores as well as specific item-level responses. These findings further support the idea that subjective cognitive concerns can emerge alongside early AD pathology, even before measurable objective impairment.[12] Our research expands on these findings from different perspectives. By focusing on item-level associations, we provide a more granular view of how specific subjective complaints relate to AD biomarkers. Importantly, both participant and study partner reports were informative, suggesting these perspectives offer complementary insights, even in the absence of overt clinical impairment.

We also found that the association of tau pathology with CFI scores, both globally and at the item level, is mostly unaffected by amyloid pathology levels above the threshold for amyloid positivity (i.e., in Aβ+ individuals) and neurodegeneration. This aligns with prior findings suggesting that SCD, as measured by CFI, defined as self-reported cognitive decline in the absence of objective deficits, may be driven by distinct biological mechanisms.[12,27] Specifically, our findings suggest that tau may influence self-awareness of cognitive change through pathways that operate independently from amyloid deposition and structural neurodegeneration. Although amyloid is considered the earliest hallmark of AD, tau burden may exert more direct effects on subjective cognitive experience. The fact that CFI scores were sensitive to tau, even when accounting for Aβ and HVa, supports the idea that multiple parallel pathways contribute to early cognitive symptoms. This insight may inform both early detection strategies and intervention timing in AD.

FIGURE 2 Odds of endorsement for Cognitive Function Index items among participants and their study partners based on Model 3. Red asterisks denote significance based on the 95% confidence interval of the odds ratio in unadjusted models, while black asterisks denote significance based on false discovery rate–adjusted *p* values.

Another objective of our study was to explore the association between the CFI score and HVa, a marker of neurodegeneration. Given that hippocampal atrophy typically emerges later in the AD continuum,[28] and because the A4 participants are all in the preclinical stage, the absence of significant associations between HVa and total CFI scores in this cohort is not surprising. We observed a similar pattern when examining HVa and item-level CFI responses. For example, participant-reported driving difficulty showed a weak but non-significant association with lower HVa. Given the hippocampus's central role in spatial memory and navigation, this finding is biologically plausible.[29,30] However, the lack of robust associations between HVa and other CFI items after adjustment suggests that hippocampal atrophy alone may not strongly predict subjective complaints in this preclinical sample. This contrasts with findings from later AD stages, during which HVa is a well-established predictor of both cognitive decline and loss of functional independence.[31,32] In our cohort, the hippocampus likely remains relatively preserved, and other processes—such as early tau deposition—may be more relevant to subjective reports. Notably, previous studies have found that SCD can predict accelerated hippocampal atrophy,[33,34] so we anticipate that longitudinal data from the A4 Study may reveal stronger associations over time. This hypothesis can be tested in future work when follow-up data are available.

The discrepancy between participant and study partner reports also highlights the importance of incorporating both perspectives when assessing early cognitive change in preclinical AD.[35] Participants may be more attuned to internal changes that are not yet observable to others, while study partners may detect more overt cognitive and functional changes. Our item-level results support this view: participant-reported concerns about memory and navigation—such as "seen a doctor for memory concerns" and "feeling lost while navigating"—were significantly associated with tau_{MTL}. Meanwhile, study partner–reported items such as "needing help remembering appointments" and "asking the same question repeatedly" showed weaker but directionally consistent trends.

Our study has a few limitations. First, because the CFI is a subjective report questionnaire, it is subject to recall bias, which may affect accuracy of responses by both participants and study partners. Inconsistent agreement between these sources may reflect differing perspectives and/or limited participant insight into specific items, highlighting the need for confirmation through multiple sources and during shorter time frames. Second, many participants in the A4 Study were White, limiting the generalizability of our findings to other racial and ethnic groups. Third, because the study design is cross-sectional, establishing causal relationships between different measures is not feasible.

Overall, our findings support that subjective reports of cognitive function can characterize early manifestations of cognitive impairment in preclinical AD trials. Future work should continue exploring item-level analysis to identify the most sensitive subjective indicators of early pathology and optimize outcome measures for preclinical AD trials.

TABLE 4 Comparison of logistic models from the Aβ+ cohort for study partner's Cognitive Function Index (CFI) items.

	Model 1		Model 2		Model 3	
	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value
Written						
Aβ	1.091 (0.849, 1.398)	0.545	1.092 (0.855, 1.392)	0.506	1.076 (0.835, 1.381)	0.625
tau_{MTL}	1.084 (0.845, 1.385)	0.545			1.064 (0.827, 1.363)	0.625
HVa			0.85 (0.626, 1.148)	0.468	0.860 (0.632, 1.165)	0.539
Social						
Aβ	1.259 (0.817, 1.903)	0.494	1.294 (0.847, 1.944)	0.513	1.246 (0.801, 1.901)	0.740
tau_{MTL}	1.164 (0.765, 1.727)	0.646			1.154 (0.754, 1.724)	0.792
HVa			0.904 (0.517, 1.568)	0.985	0.936 (0.531, 1.629)	0.970
Repeat						
Aβ	1.411 (1.042, 1.908)	0.081	1.542 (1.147, 2.074)	**0.014**	1.439 (1.058, 1.953)	0.066
tau_{MTL}	1.33 (0.985, 1.786)	0.100			1.363 (1.003, 1.847)	0.090
HVa			1.100 (0.740, 1.638)	0.742	1.182 (0.792, 1.767)	0.471
Active						
Aβ	1.145 (0.691, 1.812)	0.808	1.163 (0.717, 1.811)	0.668	1.092 (0.652, 1.742)	0.828
tau_{MTL}	1.297 (0.809, 2.002)	0.808			1.232 (0.765, 1.917)	0.828
HVa			0.646 (0.338, 1.208)	0.616	0.682 (0.356, 1.275)	0.828
Concern						
Aβ	1.055 (0.703, 1.533)	0.843	1.048 (0.708, 1.503)	0.939	1.041 (0.690, 1.516)	0.959
tau_{MTL}	1.04 (0.693, 1.506)	0.843			1.025 (0.683, 1.488)	0.959
HVa			0.863 (0.535, 1.388)	0.763	0.867 (0.534, 1.397)	0.894
Recall						
Aβ	1.527 (1.193, 1.970)	**0.006**	1.536 (1.207, 1.972)	**0.004**	1.529 (1.193, 1.976)	**0.007**
tau_{MTL}	1.019 (0.794, 1.300)	0.879			1.021 (0.794, 1.307)	0.925
HVa			1.011 (0.748, 1.366)	0.944	1.015 (0.749, 1.375)	0.925
Appliance						
Aβ	1.016 (0.563, 1.702)	0.956	1.144 (0.653, 1.88)	0.987	1.028 (0.566, 1.736)	0.981
tau_{MTL}	1.498 (0.904, 2.385)	0.343			1.518 (0.908, 2.451)	0.380
HVa			0.993 (0.501, 1.956)	0.987	1.094 (0.554, 2.158)	0.981
Follow						
Aβ	1.351 (0.935, 1.934)	0.239	1.415 (0.991, 2.007)	0.123	1.326 (0.910, 1.911)	0.357
tau_{MTL}	1.29 (0.899, 1.825)	0.240			1.269 (0.882, 1.805)	0.371
HVa			0.833 (0.51, 1.348)	0.536	0.876 (0.535, 1.421)	0.609
Lost						
Aβ	1.382 (1.008, 1.886)	0.145	1.423 (1.048, 1.929)	0.079	1.353 (0.984, 1.853)	0.237
tau_{MTL}	1.293 (0.937, 1.763)	0.253			1.244 (0.899, 1.705)	0.341
HVa			0.729 (0.479, 1.098)	0.311	0.767 (0.503, 1.160)	0.341
Help						
Aβ	1.13 (0.823, 1.533)	0.512	1.269 (0.94, 1.701)	0.266	1.136 (0.826, 1.546)	0.583
tau_{MTL}	1.589 (1.181, 2.142)	**0.005**			1.600 (1.184, 2.172)	**0.008**
HVa			0.952 (0.647, 1.399)	0.908	1.052 (0.713, 1.553)	0.797

(Continues)

TABLE 4 (Continued)

	Model 1		Model 2		Model 3	
	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value	Odds ratio	FDR-adjusted *p* value
Memory						
Aβ	1.426 (1.045, 1.941)	0.056	1.418 (1.045, 1.921)	0.082	1.379 (1.004, 1.886)	0.118
tau_{MTL}	1.182 (0.858, 1.608)	0.517			1.122 (0.811, 1.533)	0.705
HVa			0.660 (0.434, 0.993)	0.085	0.678 (0.444, 1.023)	0.135
Misplace						
Aβ	1.12 (0.861, 1.45)	0.547	1.105 (0.855, 1.421)	0.565	1.107 (0.849, 1.436)	0.644
tau_{MTL}	1.005 (0.772, 1.297)	0.969			0.991 (0.760, 1.283)	0.948
HVa			0.893 (0.649, 1.226)	0.565	0.892 (0.645, 1.228)	0.644
Money						
Aβ	1.295 (0.791, 2.067)	0.403	1.353 (0.842, 2.133)	0.435	1.262 (0.760, 2.038)	0.562
tau_{MTL}	1.308 (0.794, 2.085)	0.403			1.281 (0.776, 2.056)	0.562
HVa			0.805 (0.414, 1.536)	0.722	0.848 (0.435, 1.620)	0.827
Drive						
Aβ	1.138 (0.811, 1.573)	0.515	1.185 (0.854, 1.622)	0.520	1.136 (0.807, 1.576)	0.601
tau_{MTL}	1.17 (0.842, 1.601)	0.471			1.168 (0.838, 1.606)	0.576
HVa			0.96 (0.632, 1.454)	0.848	0.988 (0.649, 1.499)	0.955
Work						
Aβ	1.259 (0.729, 2.095)	0.677	1.379 (0.821, 2.250)	0.721	1.241 (0.714, 2.073)	0.787
tau_{MTL}	1.54 (0.957, 2.424)	0.224			1.510 (0.933, 2.386)	0.320
HVa			0.747 (0.387, 1.407)	0.742	0.798 (0.414, 1.506)	0.787

Note: All models were adjusted for *APOE* ε4 status, sex, age, and education. Model 1 included Aβ and tau SUVR in the MTL as continuous variables, Model 2 included Aβ and hippocampal volume as continuous variables, and Model 3 included Aβ and tau SUVR in the MTL as continuous variables.
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; FDR, false discovery rate; HVa, adjusted hippocampal volume; MTL, medial temporal lobe; SUVR, standardized uptake value ratio; tau_{MTL}, tau standardized uptake value ratios in medial temporal lobe.

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CONFLICT OF INTEREST STATEMENT

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Amgen. Dr. Lipton serves on the editorial board of *Neurology*, is a senior advisor to *Headache*, and an associate editor for *Cephalalgia*. He has served as a reviewer for the NIA and NINDS. He holds stock or stock options in Axon, Biohaven Holdings, CoolTech, and Manistee. He serves as a consultant, advisory board member, or has received honoraria from: AbbVie (Allergan), American Academy of Neurology, American Headache Society, Amgen, Avanir, Axon, Axsome, Biohaven, Biovision, Boston Scientific, Dr. Reddy's (Promius), Electrocore, Eli Lilly, eNeura Therapeutics, Equinox, GlaxoSmithKline, Grifols, Lundbeck (Alder), Manistee, Merck, Pernix, Pfizer, Satsuma, Supernus, Teva, Trigemina, Vector, and Vedanta. He receives royalties from *Wolff's Headache*, 7th and 8th editions (Oxford University Press, Wiley, and Informa). The other co-authors report no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

This study used publicly available data that does not require informed consent from individual participants. Therefore, informed consent was not necessary for this research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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