Received: 14 February 2024 | Revised: 24 June 2024 | Accepted: 24 July 2024

DOI: 10.1002/dad2.70047

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Clinical and demographic factors modify the association between plasma phosphorylated tau-181 and cognition

Corey J. Bolton[1,2] | **Marilyn Steinbach**[1,3] | **Omair A. Khan**[1,4] | **Dandan Liu**[1,4] | **Julia O'Malley**[1,3] | **Logan Dumitrescu**[1,3] | **Amalia Peterson**[1,3] | **Angela L. Jefferson**[1,3] | **Timothy J. Hohman**[1,3] | **Henrik Zetterberg**[5,6,7,8,9,10] | **Katherine A. Gifford**[1,3] | **for the Alzheimer's Disease Neuroimaging Initiative**

[1]Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[3]Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[5]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden

[6]Clinical Neurochemistry Lab, Sahlgrenska University Hospital, Mölndal, Sweden

[7]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[8]UK Dementia Research Institute, University College London, London, UK

[9]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

[10]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

Correspondence
Katherine Gifford, Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, 1207 17th Avenue South, Suite 204, Nashville, TN 37212, USA.
Email: katie.gifford@vumc.org

Alzheimer's Disease Neuroimaging Initiative (ADNI) data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of

Abstract

INTRODUCTION: Plasma phosphorylated tau-181 (p-tau181) associations with global cognition and memory are clear, but the link between p-tau181 with other cognitive domains and subjective cognitive decline (SCD) across the clinical spectrum of Alzheimer's disease (AD) and how this association changes based on genetic and demographic factors is poorly understood.

METHODS: Participants were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and included 1185 adults >55 years of age with plasma p-tau181 and neuropsychological test data. Linear regression models related plasma p-tau181 to neuropsychological composite and SCD scores with follow-up models examining

Funding information: Swedish Research Council, Grant/Award Numbers: #2022-01018, #2019-02397; European Union's Horizon Europe research and innovation programme, Grant/Award Number: 101053962; Swedish State Support for Clinical Research, Grant/Award Number: #ALFGBG-71320; Alzheimer Drug Discovery Foundation, Grant/Award Number: #201809-2016862; Alzheimer's Association AD Strategic Fund, Grant/Award Numbers: #ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C; Bluefield Project; Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden, Grant/Award Number: FO2022-0270; Marie Skłodowska-Curie, Grant/Award Number: 860197; MIRIADE; European Union Joint Programme – Neurodegenerative Disease Research, Grant/Award Number: JPND2021-00694; National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre; UK Dementia Research Institute at UCL, Grant/Award Number: UKDRI-1003; National Institutes of Health, Grant/Award Number: U01 AG024904; Department of Defense, Grant/Award Number: W81XWH-12-2-0012; National Institute on Aging, Grant/Award Numbers: K23-AG045966, R01-AG062826, R01-AG073439, F32-AG076276, K24-AG046373, T32-AG058524; National Institute of Biomedical Imaging and Bioengineering; Canadian Institutes of Health Research; Foundation for the National Institutes of Health; Northern California Institute for Research and Education

ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

plasma p-tau181 interactions with cognitive diagnosis, apolipoprotein E *(APOE)* ε4 carrier status, age, and sex on cognitive outcomes.

RESULTS: Higher plasma p-tau181 level was associated with worse memory, executive functioning, and language abilities, and greater informant-reported SCD. Visuospatial abilities and self-report SCD were not associated with plasma p-tau181. Associations were generally stronger in mild cognitive impairment (MCI) or dementia, *APOE* ε4 carriers, women, and younger participants.

DISCUSSION: Higher levels of plasma p-tau181 are associated with worse neuropsychological test performance across multiple cognitive domains; however, these associations vary based on disease stage, genetic risk status, age, and sex.

KEYWORDS
ADNI, Alzheimer's disease, dementia, mild cognitive impairment, plasma p-tau181

Highlights

- Greater plasma p-tau181 was associated with lower cognition across most domains.
- Associations between p-tau181 and cognition were modified by age and sex.
- Level of p-tau181 was more strongly associated with cognition in people with mild cognitive impairment (MCI) and apolipoprotein E (*APOE*) ε4.

1 | INTRODUCTION

Advancements in Alzheimer's disease (AD) therapies have necessitated early and accurate detection of AD pathology to initiate treatment prior to widespread neuronal loss. Blood-based biomarkers for phosphorylated tau (p-tau) have emerged as accessible and specific biomarkers for AD pathology. Plasma levels of tau phosphorylated at threonine 181 (plasma p-tau181) are highly correlated with cerebrospinal fluid (CSF) levels of p-tau181,[1] associated with amyloid and tau deposition on positron emission tomography (PET) imaging,[2,3] relate to neurodegeneration in AD-specific brain regions on volumetric imaging,[4] and accurately differentiate AD from other neurodegenerative conditions.[1,3] Due to its promise in identifying AD pathological changes, this biomarker has the potential for integration into clinical settings for the screening and diagnosis of AD.[5]

Although plasma phosphorylated tau-181 (p-tau181) appears to reflect the underlying pathology of AD, its associations with clinical outcomes are less understood. Past work has identified associations between plasma p-tau181 on cognitive screening measures or isolated measures of memory functioning.[3,4] However, there has been little work examining more subtle changes in cognition or patterns of cognitive decline across neuropsychological domains. Identifying domains of cognition (e.g., episodic memory, executive functioning) that are affected can provide valuable information related to the localization of pathological changes, thereby further elucidating the clinicopathological correlates of this novel biomarker.[6] In addition, it is not yet known how associations between plasma p-tau181 and cognition may be modified by demographic data (e.g., age, sex), disease state (mild cognitive impairment [MCI], dementia), or genetic factors (e.g., apolipoprotein E *[APOE]* ε4 carrier status), which are known to be associated with cognition in aging.[7–9]

This study investigates associations between plasma p-tau181 and comprehensive assessment of objective and subjective cognition. Results will elucidate how this novel biomarker relates to specific clinical changes across various disease states and demographic groups. We hypothesize that plasma p-tau181 will be most strongly associated with memory and executive functions, consistent with a typical AD clinical syndrome,[10] with stronger associations in individuals at increased risk of clinical AD (e.g., *APOE* ε4 carriers, individuals with MCI).

2 | METHODS

2.1 | Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Data were obtained from the ADNI database (https://www.loni.ucla.edu/ADNI/Data/ADCS_Download.jsp) in November 2021 and included participants from cohorts ranging from ADNI 1 to ADNI 3. Participants 55–90 years of age were recruited from across the United States and Canada and were excluded if they had a Hachinski ischemic score[11] >4,

Geriatric Depression Scale (GDS)[12] score ≥6, no study partner, contraindications to MRI, did not speak English or Spanish fluently, were not in good physical health, or used drugs with anticholinergic or opioid properties. Cognitively unimpaired (CU) participants had no memory complaints, normal memory function (assessed using delayed paragraph recall of the Wechsler Memory Scale—Revised; WMS-R)[13] and Mini-Mental State Examination (MMSE)[14] ≥24, Clinical Dementia Rating (CDR)[15] global score of 0, and absence of significant impairment in cognitive and functional performance. Participants with MCI had memory complaints (by self-report or from a study partner), abnormal memory functioning (>1 SD below the normative sample on WMS-R) and MMSE ≥24, CDR global score of 0.5, and sufficient cognitive and functional performance so as to prevent diagnosis of dementia. Participants with dementia had memory complaints, abnormal memory function, and MMSE between 20 and 26, CDR global score of 0.5–1.0, and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD.[16] (For more information, see www.adni-info.org.) Participants without usable plasma p-tau181 or covariate data were excluded. Participants often have cognitive data at several epochs prior to the collection of plasma samples. We used cognitive data from the visit when plasma p-tau was first quantified. Diagnosis was coded at each visit and the diagnosis from the visit in which plasma was collected was used for analyses.

2.2 | Neuropsychological measures

Participants completed the comprehensive neuropsychological assessment of memory, executive functioning, language, and visuospatial abilities using the ADNI neuropsychological protocol. Domain-based composite scores were utilized. These composite scores were developed previously using item response theory and latent variable modeling to minimize the possibility of multiple comparisons from similar assessments. The memory composite[17] included the Rey Auditory Verbal Learning Test (RAVLT),[18] ADAS-Cog[19] word list and word recognition, WMS-R Logical Memory,[13] and MMSE[14] word recall. The executive functioning composite[20] included Category Fluency,[21] Trail Making Tests Part A and B,[22] Digit Span Backwards,[23] Digit Symbol Substitution,[23,] and clock drawing.[24] The visuospatial composite[25] included clock drawing, the interlocking pentagons of the MMSE,[14] and the constructional praxis item on ADAS-Cog. The language composite included the Boston Naming Test (BNT)[26]; Category Fluency; the MMSE's object naming, sentence repetition, reading, and writing, and following a three-step command; ADAS-Cog commands, object naming, and ideational praxis; and the Montreal Cognitive Assessment (MoCA) phonemic fluency and sentence repetition.[27] Single-factor models constructed using Mplus or R were used to create each composite; models were fit to the data, which was assessed using confirmatory fit index, Tucker–Lewis index, and root mean squared error of approximation. These models were completed by ADNI and resulting composite scores were downloaded. Higher composite scores indicate better test performance.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Although plasma p-tau biomarkers are relatively novel, there have been several recent publications describing the predictive validity of these biomarkers. These relevant citations are appropriately cited.
2. **Interpretation**: The association between plasma p-tau181 and both objective and subjective cognition is modified by disease stage, genetic risk status, age, and sex.
3. **Future directions**: Future work should extend these findings to include other novel plasma biomarkers of AD and related dementias and examine associations longitudinally to further advance a precision medicine approach to fluid biomarkers in which the right biomarkers are chosen for the right patient, at the right time.

2.3 | Subjective cognitive decline

Participants and their loved ones completed the Everyday Cognition (ECog) questionnaire as a measure of self- and informant-reported subjective cognitive decline (SCD). The 39-item ECog questionnaire assesses functional abilities linked to different cognitive domains (memory, language, and executive functioning) compared to 10 years prior using a 5-point scale, with higher scores indicating greater SCD.[28]

2.4 | Fluid collection and biochemical analyses

Participants completed a venous blood draw at a standard time of day (8:00 a.m.) following an overnight fast (minimum 6 h). Blood was collected in two 10 mL ethylenediaminetetraacetic acid (EDTA) purple top tubes and centrifuged within 1 h of collection. Plasma was pipetted into a 13 mL polypropylene transfer tube and then immediately frozen in dry ice and shipped the same day to ADNI Core Laboratories, where it was stored at −80°C. Plasma p-tau181 concentration was measured using Single molecule array (Simoa) technology, using an in-house assay developed by the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden, described fully elsewhere.[3]

2.5 | Statistical analyses

Linear regression models with ordinary least square estimates related plasma p-tau181 to objective and subjective cognition outcomes. Covariates were selected a priori based on their potential to confound analytical models due to their known associations with objective

TABLE 1 Participant characteristics.

	Combined ($n = 1185$)	CU ($n = 406$)	MCI ($n = 560$)	Dementia ($n = 219$)	p-value
Age, years	74.3 ± 7.6	75.0 ± 6.6	73.1 ± 7.9	76.0 ± 7.9	**< 0.001**
Sex, % male	54	47	58	59	**0.001**
Education, years	16.2 ± 2.7	16.5 ± 2.6	16.1 ± 2.7	15.9 ± 2.8	**0.007**
APOE ε4, % carrier	43	28	46	67	**< 0.001**
Plasma p-tau181, pg/mL	18.3 ± 10.9	15.4 ± 10.5	18.3 ± 11.2	23.6 ± 8.8	**< 0.001**
MoCA, total score	24.2 ± 5.1	27.2 ± 2.7	24.6 ± 3.7	17.4 ± 5.4	**< 0.001**
Memory, *z*-score	0.3 ± 0.8	0.9 ± 0.5	0.3 ± 0.6	−0.9 ± 0.4	**< 0.001**
Executive functions, *z*-score	0.4 ± 0.7	0.7 ± 0.5	0.4 ± 0.5	−0.5 ± 0.7	**< 0.001**
Language, *z*-score	0.4 ± 0.6	0.8 ± 0.5	0.4 ± 0.5	−0.3 ± 0.6	**< 0.001**
Visuospatial, *z*-score	0.0 ± 0.4	0.1 ± 0.3	0.5 ± 0.3	−0.3 ± 0.6	**< 0.001**
ECog self, total score	63.5 ± 21.4	54.2 ± 12.7	69.2 ± 20.5	66.2 ± 29.2	**< 0.001**
ECog informant, total score	66.5 ± 30.5	45.4 ± 12.4	65.3 ± 23.4	108.2 ± 27.8	**< 0.001**

Note: Values are denoted as mean ± SD or frequency.
Bold font indicates p-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; CU, cognitively unimpaired; ECog; Everyday Cognition questionnaire; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment.

and subjective cognition, including age,[29] sex,[30] education[31], cognitive diagnosis,[32] and *APOE* ε4 carrier status (defined as having at least one *APOE* ε4 allele).[33] To account for changes in p-tau181 levels in different clinical and demographic groups, subsequent models evaluated *plasma p-tau181 × cognitive diagnosis*, *p-tau181 × APOE ε4 carrier status*, *p-tau181 × age*, and *p-tau181 × sex* interactions on objective and subjective cognition. Significance was set a priori at $p < 0.05$. Sensitivity analyses were performed by removing outliers > SD from mean values to assess whether outliers accounted for results. Additional sensitivity analyses were conducted for ECog outcomes using a mean score rather than a sum of scores to determine if score quantification accounted for results. Multiple comparison correction was performed for each analytical set using a false discovery rate (FDR) based on the Benjamini–Hochberg procedure.[34] Analyses were conducted using R 3.4.2 (www.r-project.org).

3 | RESULTS

Participants included 1185 adults ages 55–94 (46% female, 44% *APOE* ε4 carriers). (See Table 1 for participant characteristics for the entire sample and stratified by cognitive diagnosis.) Participants were also divided by *APOE* ε4 carrier status, age (using a median split), and sex for stratified analyses. *APOE* ε4 carriers, compared to noncarriers, were younger; more likely to have MCI or dementia; performed worse on memory, executive functions, and language composite measures; had higher p-tau181 levels; and had greater self- and informant-reported SCD. Compared to the younger age group, the older group was more likely to be male; less likely to be *APOE* ε4 carriers; more likely to have dementia over MCI; performed worse on memory, executive functions, and language composite measures; had more p-tau181; and had greater informant-reported SCD. Women, compared to men, were more likely to be CU, have less education, be younger, perform better on memory composite, have lower p-tau181, and have lower self- and informant-reported SCD.

3.1 | Plasma p-tau181 and cognition

In the entire sample, higher p-tau181 levels were associated with lower scores on memory ($\beta = -0.008$, p-value < 0.001), executive functioning ($\beta = -0.005$, p-value = 0.002), and language ($\beta = -0.004$, p-value = 0.006) composite scores, but not on visuospatial functioning ($\beta = -0.001$, p-value = 0.47). In addition, higher p-tau181 levels were associated with higher informant-reported SCD ($\beta = 0.17$, p-value = 0.007) but not with self-reported SCD ($\beta = 0.07$, p-value = 0.59). Results were comparable after FDR correction. (See Table 2 for the results of main effects analyses.)

3.2 | Plasma p-tau181 × cognitive diagnosis and cognition

Level of p-tau181 interacted with diagnosis in predicting memory ($\beta = -0.001$, p-value < 0.001), executive functioning ($\beta = -0.01$, p-value = 0.01), language ($\beta = -0.009$, p-value = 0.05), and informant-report SCD ($\beta = -0.51$, p-value = 0.03), but not on visuospatial composite score or self-reported SCD (p-values > 0.12). Models stratified by diagnosis revealed that these associations were driven by MCI and dementia participants. Higher p-tau181 level was associated with lower performance on memory ($\beta = -0.01$, p-value < 0.001), executive functioning ($\beta = -0.005$, p-value = 0.01), and language ($\beta = -0.008$, p-value = 0.02) composites in participants with MCI as well as lower executive functioning ($\beta = -0.03$, p-value = 0.008) and language

TABLE 2 Plasma p-tau181 associations with cognitive and SCD outcomes.

	B	95% Confidence intervals	*p*-value
Memory	−0.008	−0.01, −0.005	**< 0.001***
Executive functions	−0.005	−0.008, −0.002	**0.002***
Language	−0.004	−0.007, −0.001	**0.008***
Visuospatial	−0.001	−0.004, 0.002	0.47
ECog self	0.07	−0.18, 0.32	0.59
ECog informant	0.17	0.05, 0.29	**0.007***

Note: Models were adjusted for age, sex, education, *APOE* ε4 status, and cognitive diagnosis.
Bold font indicates *p*-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; CU, cognitively unimpaired; ECog, Everyday Cognition questionnaire; FDR, false discovery rate; MCI, mild cognitive impairment.
*FDR-corrected *p*-value < 0.05.

(β = −0.02, *p*-value = 0.03) composite scores and higher informant-reported SCD (β = 0.52, *p*-value = 0.02) scores in participants with dementia. Results were comparable after FDR correction. See Table 3 for results stratified by diagnosis and Figure 1 for illustrations of stratified analyses.

3.3 | Plasma p-tau181 × *APOE* ε4 carrier status and cognition

Level of p-tau181 interacted with *APOE* ε4 carrier status in predicting memory (β = −0.006, *p*-value = 0.02) and executive functioning (β = −0.006, *p*-value = 0.05) composite scores; however, these results did not persist after FDR correction. Level of p-tau181 did not interact with *APOE* ε4 carrier status on language (β = −0.005, *p*-value = 0.07), visuospatial (β = −0.007, *p*-value = 0.58), self-reported SCD (β = 0.16, *p*-value = 0.49), or informant-reported SCD (β = 0.18, *p*-value = 0.13) scores. (See Table 4 for results stratified by *APOE* ε4 carrier status.)

3.4 | Plasma p-tau181 × age and cognition

Level of p-tau181 interacted with age on memory (β = 0.0004, *p*-value = 0.005) and executive functioning (β = 0.0004, *p*-value = 0.02) composite scores, but not on other outcomes (*p*-values > 0.10). Models stratified by age showed that higher p-tau181 levels were associated with lower scores on memory (β = −0.01, *p*-value < 0.001), executive functioning (β = −0.01, *p*-value < 0.001), and language (β = −0.007, *p*-value = 0.001) composite scores and informant-reported SCD (β = 0.17, *p*-value = 0.05) in younger participants. Higher p-tau181 levels were also associated with worse memory performance in older participants (β = −0.006, *p*-value < 0.001), although to a lesser degree than in younger participants. Results were comparable after FDR correction. (See Table 5 for results stratified by age group and Figure 2 for illustrations of stratified analyses.)

3.5 | Plasma p-tau181 × sex and cognition

Level of p-tau181 interacted with sex on memory composite score (β = −0.006, *p*-value = 0.03) and self-reported SCD scores (β = −0.68, *p*-value = 0.02). However, these results were attenuated after FDR correction (*p*-values > 0.06). In models stratified by sex, higher p-tau181 levels were associated with lower memory in both men (β = −0.006, *p*-value = 0.002) and women (β = −0.009, *p*-value = 0.0001), with stronger associations in women. Higher p-tau181 levels were also associated with greater informant-reported SCD scores in men (β = 0.23, *p*-value = 0.005), but not in women (*p*-value = 0.46), and with executive function composite scores in women (β = −0.006, *p*-value = 0.01), but not in men (*p*-value = 0.06). All stratified results persisted after FDR correction. (See Table 6 for results stratified by sex and Figure 3 for illustrations of stratified analyses.)

3.6 | Sensitivity analyses

Results across all analyses were largely unchanged after excluding outliers and using mean scores, rather than total scores, for all SCD analyses.

4 | DISCUSSION

Among community-dwelling older adults across the AD clinical spectrum, higher levels of plasma p-tau181 were associated with lower cognitive performance in the domains of memory, executive functioning, and language, and greater informant-reported SCD. Visuospatial abilities and self-report SCD were not associated with plasma p-tau181. Results were most prominent in individuals who were diagnosed with MCI or dementia, *APOE* ε4 carriers, women, and younger in age. Plasma p-tau181 was not associated with objective or subjective cognition in CU individuals.

The observed associations between plasma p-tau181 and cognition align with past work in support of plasma p-tau181 as a marker of AD neurodegeneration.[4] Plasma p-tau181 was robustly associated with episodic memory functioning, the earliest and most typical cognitive deficit seen in AD resulting from the formation of neurofibrillary tangles and subsequent atrophy in memory-critical structures of the medial temporal lobes. In addition, aligning with recently published work,[35] plasma p-tau181 was associated with language and executive functioning, cognitive domains that become impaired due to evolving neurodegeneration in the frontal and temporal association cortices secondary to pathological progression of AD.[36] These patterns were strongest in individuals with MCI or dementia and in *APOE* ε4 carriers. The diagnostic association is likely due to the fact that people in preclinical or dementia states of AD evidence the highest levels of plasma p-tau181[1] and lowest levels of cognition, and the current results lend further support to the validity of plasma p-tau181 as a clinical marker of AD. Of note, p-tau181 was not associated with memory in dementia likely due to the ubiquity of memory problems at this stage of cognitive impairment and plateauing levels of p-tau181 in advanced disease.[2] Similarly, *APOE* ε4 is associated with worse memory and reasoning in

TABLE 3 Plasma p-tau181 × diagnosis interactions on cognitive and SCD outcomes.

	p-tau × *diagnosis*		CU ($n = 406$)		MCI ($n = 560$)		Dementia ($n = 219$)	
	B	***p*-value**	***β***	***p*-value**	***β***	***p*-value**	***β***	***p*-value**
Memory	0.001	**< 0.001***	−0.002	0.36	−0.01	**<0.001***	−0.002	0.47
Executive functions	−0.01	**0.01***	0.001	0.55	−0.005	**0.01***	−0.02	**0.008***
Language	−0.009	**0.05**	0.0002	0.94	−0.004	**0.02***	−0.01	**0.03**
Visuospatial	−0.003	0.75	0.001	0.54	−0.001	0.41	−0.002	0.68
ECog self	−0.53	0.13	0.10	0.37	0.14	0.43	−0.23	0.61
ECog informant	0.51	**0.03**	0.009	0.90	0.18	0.07	0.52	**0.02***

Note: Models were adjusted for age, sex, education, and *APOE* ε4 status.
Bold font indicates *p*-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; CU, cognitively unimpaired; ECog, Everyday Cognition questionnaire; FDR, false discovery rate; MCI, mild cognitive impairment.
*FDR-corrected *p*-value < 0.05.

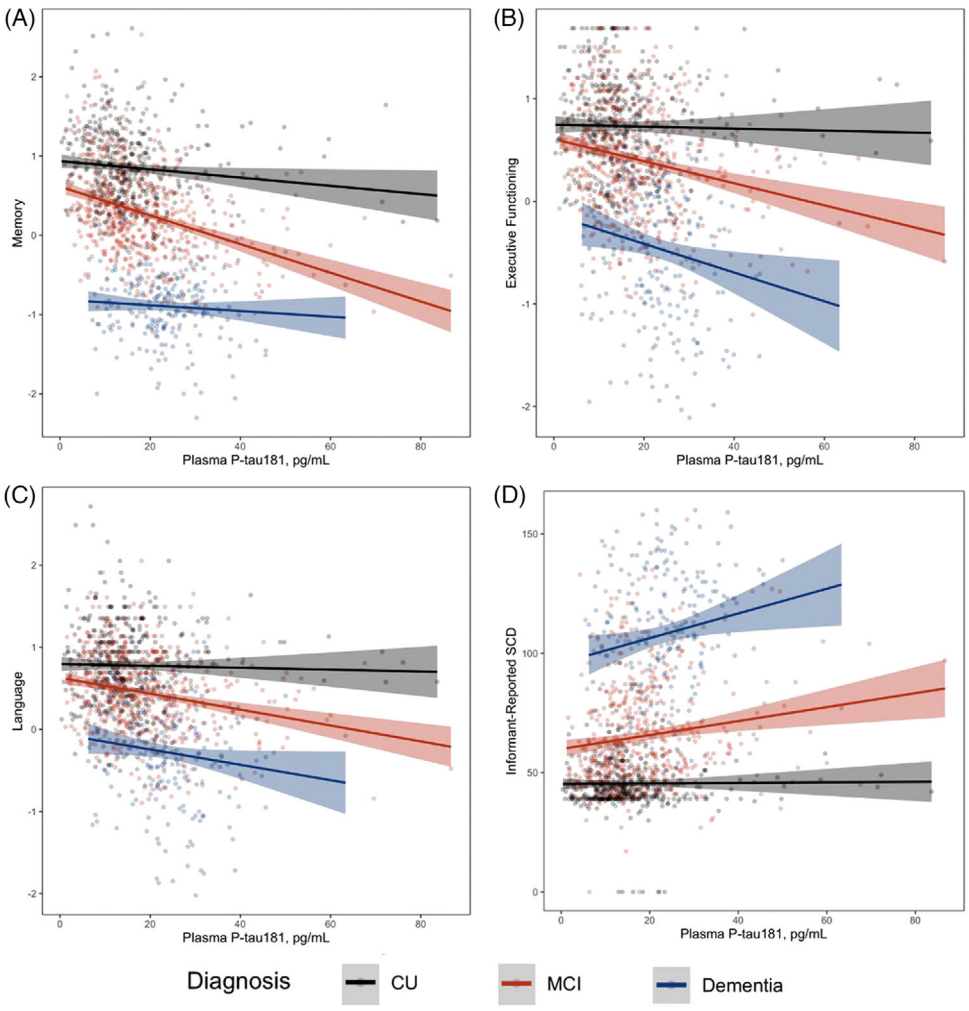

FIGURE 1 Plasma p-tau181 × cognitive diagnosis interactions on cognitive outcomes. Lines reflect cognitive domain or informant-reported SCD scores corresponding to plasma p-tau181 levels. Shading reflects 95% confidence interval. (A) Associations between plasma p-tau181 levels and memory composite score, stratified by cognitive diagnosis: CU $\beta = -0.002$, $p = 0.36$; MCI $\beta = -0.01$, $p < 0.001$; and dementia $\beta = -0.002$, $p = 0.47$. (B) Associations between plasma p-tau181 levels and executive functioning composite score, stratified by cognitive diagnosis: CU $\beta = 0.001$, $p = 0.55$; MCI $\beta = -0.005$, $p = 0.01$; and dementia $\beta = -0.02$, $p = 0.008$. (C) Associations between plasma p-tau181 levels and language composite score, stratified by cognitive diagnosis: CU $\beta = 0.0002$, $p = 0.94$; MCI $\beta = -0.004$, $p = 0.02$; and dementia $\beta = -0.01$, $p = 0.03$. (D) Associations between plasma p-tau181 levels and informant-reported SCD score, stratified by cognitive diagnosis: CU $\beta = 0.0009$, $p = 0.90$; MCI $\beta = 0.18$, $p = 0.07$; and dementia $\beta = 0.52$, $p = 0.02$. CU, cognitively unimpaired; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

TABLE 4 Plasma p-tau181 × *APOE* ε4 status interactions on cognitive and SCD outcomes.

	p-tau × *APOE ε4 status*		ε4 negative (*n* = 671)		ε4 positive (*n* = 516)	
	B	*p*-value	*β*	*p*-value	*β*	*p*-value
Memory	−0.006	**0.02**	−0.004	**0.02**	−0.01	**< 0.001***
Executive functions	−0.006	**0.05**	−0.002	0.35	−0.008	**< 0.001***
Language	−0.005	0.07	−0.002	0.36	−0.006	**0.003***
Visuospatial	−0.002	0.58	−0.0004	0.85	−0.002	0.44
ECog self	0.16	0.49	−0.06	0.66	0.18	0.47
ECog informant	0.18	0.13	0.07	0.34	0.27	**0.01***

Note: Models were adjusted for age, sex, education, and cognitive diagnosis.
Bold font indicates *p*-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; ECog, Everyday Cognition questionnaire; FDR, false discovery rate.
*FDR-corrected *p*-value < 0.05.

TABLE 5 Plasma p-tau181 × age interactions on cognitive and SCD outcomes.

	p-tau × *age*		Age <75 years (*n* = 594)		Age ≥75 years (*n* = 592)	
	β	*p*-value	*β*	*p*-value	*β*	*p*-value
Memory	0.0004	**0.005***	−0.01	**< 0.001***	−0.006	**< 0.001***
Executive functions	0.0004	**0.02**	−0.01	**< 0.001***	−0.001	0.47
Language	0.0001	0.43	−0.007	**0.001***	−0.003	0.12
Visuospatial	0.0002	0.23	−0.004	0.12	0.001	0.68
ECog self	−0.03	0.11	0.22	0.58	−0.02	0.91
ECog informant	−0.01	0.19	0.17	**0.05**	0.16	0.07

Note: Models were adjusted for age, sex, education, *APOE* ε4 status, and cognitive diagnosis.
Bold font indicates *p*-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; ECog, Everyday Cognition questionnaire; FDR, false discovery rate.
*FDR-corrected *p*-value < 0.05.

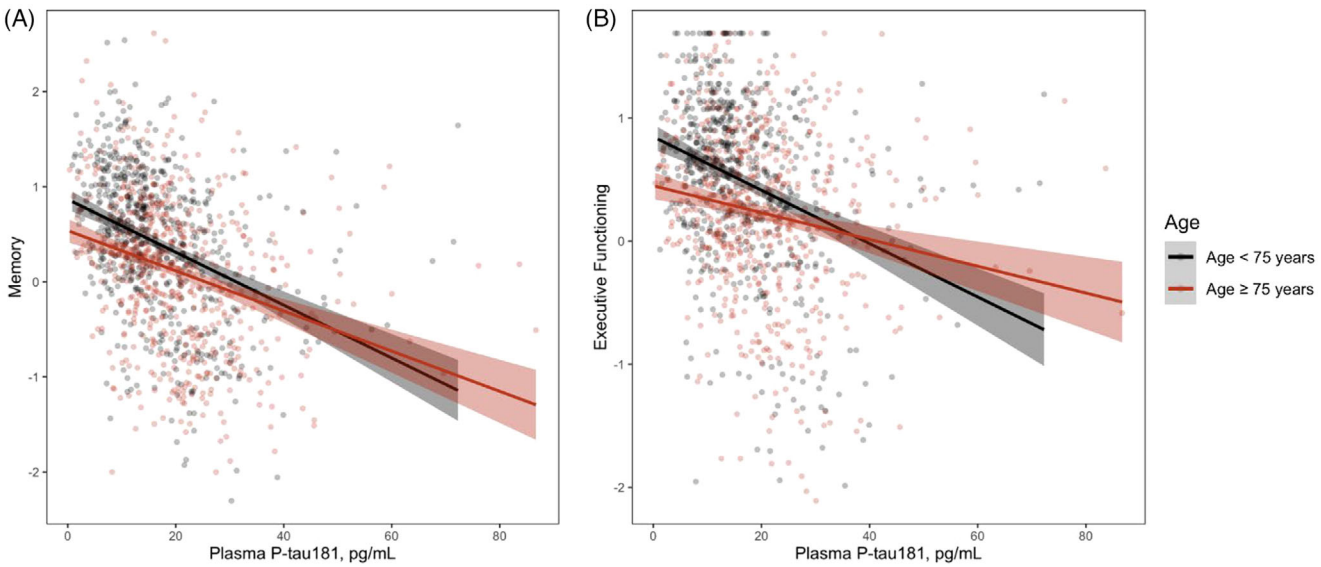

FIGURE 2 Plasma p-tau181 × age interactions on cognitive outcomes. Lines reflect cognitive domain scores corresponding to plasma p-tau181 levels. Shading reflects 95% confidence interval. (A) Associations between plasma p-tau181 levels and memory composite score, stratified by age group: <75 years $\beta = -0.01$, $p < 0.001$; ≥75 years $\beta = -0.006$, $p < 0.001$. (B) Associations between plasma p-tau181 levels and executive functioning composite score, stratified by age group: <75 years $\beta = -0.01$, $p < 0.001$; ≥75 years $\beta = -0.001$, $p = 0.47$.

TABLE 6 Plasma p-tau181 × sex interactions on cognitive and SCD outcomes.

	p-tau x sex		Male ($n = 644$)		Female ($n = 543$)	
	B	***p*-value**	***β***	***p*-value**	***β***	***p*-value**
Memory	−0.006	**0.03**	−0.006	**0.002***	−0.009	**0.0001***
Executive functioning	−0.002	0.48	−0.004	0.06	−0.006	**0.01***
Language	−0.0001	0.97	−0.004	0.06	−0.004	0.07
Visuospatial	0.0002	0.95	−0.0009	0.63	−0.002	0.50
ECog self	−0.68	**0.02**	0.20	0.18	−0.46	0.07
ECog informant	−0.07	0.57	0.23	**0.005***	0.07	0.46

Note: Models were adjusted for age, education, *APOE* ε4 status, and cognitive diagnosis.
Bold font indicates *p*-value < 0.05.
Abbreviations: *APOE*, apolipoprotein E; ECog, Everyday Cognition questionnaire; FDR, false discovery rate.
*FDR-corrected *p*-value < 0.05.

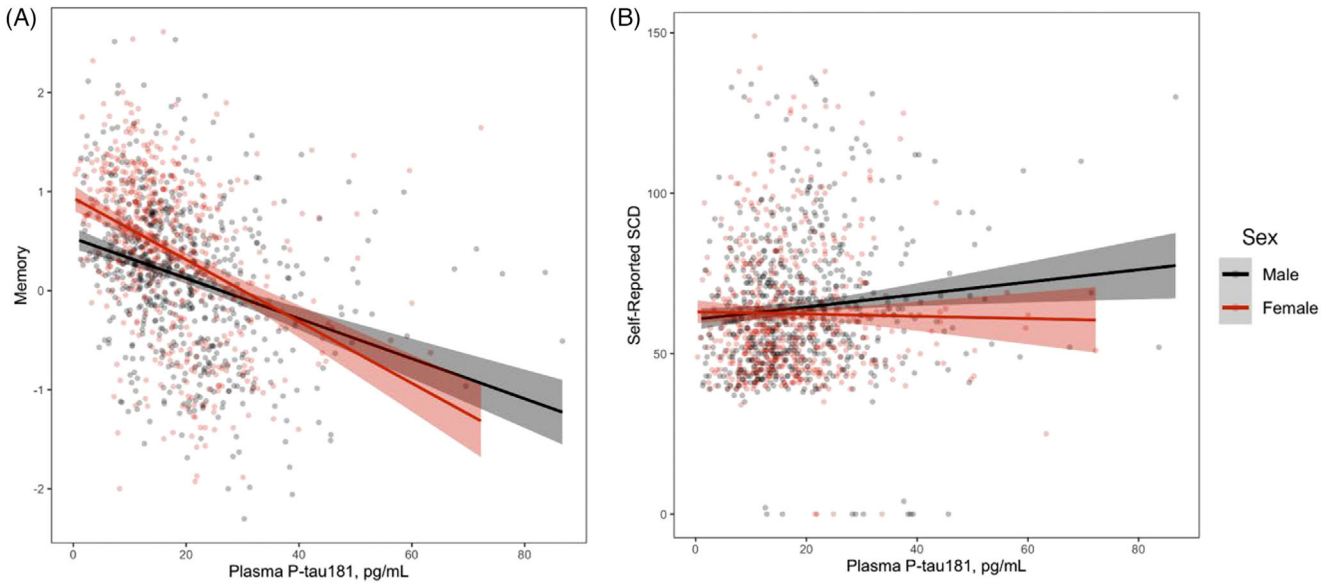

FIGURE 3 Plasma p-tau181 × sex interactions on cognitive outcomes. Lines reflect cognitive domain and self-reported SCD scores corresponding to plasma p-tau181 levels. Shading reflects 95% confidence interval. (A) Associations between plasma p-tau181 levels and memory composite score, stratified by sex: male $\beta = -0.006$, $p = 0.002$; female $\beta = -0.009$, $p = 0.0001$. (B) Associations between plasma p-tau181 levels and self-reported SCD score, stratified by sex: male $\beta = 0.20$, $p = 0.18$; female $\beta = -0.46$, $p = 0.07$. SCD, subjective cognitive decline.

older adults,[37] as well as a higher accumulation rate of tau in AD.[38] As such, *APOE* ε4 carriers can be more prone to neurodegeneration and current results suggest that *APOE* may be an important consideration when understanding how this plasma biomarker predicts who may display or develop cognitive impairment.

The lack of association between plasma p-tau181 and cognition in CU individuals was somewhat surprising given that plasma p-tau181 elevates early in the disease process, purportedly shortly after abnormal amyloid beta (Aβ) accumulation.[2] Multiple factors may be contributing to the observed findings. First, it is possible that although plasma p-tau181 can be elevated early in the disease course, the variance of either the biomarker or cognitive performances observed in this CU sample was not sufficient to observe differences. As discussed elsewhere,[39] the selection criteria for the ADNI cohorts limits the presence of comorbidities or alternative etiologies (e.g., cerebrovascular disease); thus the sample here is likely healthier than the general population. With fewer medical comorbidities, CU individuals may be less likely to have other non-AD pathologies such as cerebrovascular disease, and thus may be more resilient to early pathological changes. Second, cognitive outcomes may lack sensitivity in identifying very early and subtle cognitive changes. Education confounds neuropsychological test performance and may protect against cognitive changes related to the earliest accumulation of AD pathology.[40] In a highly educated cohort, such as this one, AD pathological changes may not produce a measurable cognitive deficit until later in the disease progression. Finally, the cross-sectional nature of this study likely limited our ability to detect an association with cognition. Similar cross-sectional studies also do not find an association between plasma

p-tau181 and cognition in CU individuals.[41–43] Plasma p-tau181 may not be sensitive to cognitive changes when measured at a single time point and prior to the preclinical stages. Rather elevated plasma p-tau181 at baseline appears to predict future cognitive decline in nondemented older adults.[44]

As expected, informant-reported SCD was associated with plasma p-tau181 within the MCI and dementia phases of AD, whereas self-reported SCD was not associated. This pattern is likely secondary to the presence of anosognosia, a common clinical feature of AD that can occur prior to frank dementia.[45] Self-reported SCD was unrelated to plasma p-tau181, even in CU participants. This finding was somewhat unexpected, as self-reported SCD has been linked with amyloid deposition, and previous findings suggest that p-tau181 elevations shortly follow increased amyloid burden.[46] This lack of association could indicate that self-reported SCD occurs prior to detectable changes in plasma p-tau181. Alternatively, self-reported SCD is present due to a multitude of factors and the null findings may be related to other etiologies driving the subjective cognitive weaknesses (e.g., mood and personality factors, learning disability).

Age and sex both appeared to modify associations between plasma p-tau181 and cognition, with stronger findings in younger participants (age <75 years) and women, likely due to multiple factors. First, with increasing age comes an increasing risk of developing other neuropathologies that contribute to cognitive changes.[47] In addition, younger age at AD onset is associated with a more aggressive disease course, greater pathological burden, and faster clinical decline.[48] Similar considerations likely occur with sex. Women may be more clinically susceptible to pathological changes of AD. For example, when comparing women and men with similar levels of AD pathology, women show greater problems with cognition across more domains as compared to men.[49] Thus, younger participants or women may be more likely to have greater cognitive impairment across more domains in the presence of AD pathology.

One unexpected finding was that, despite plasma p-tau181 being more strongly associated with cognition in women, it was associated with greater informant-reported SCD in men, but not women. These findings are previously unreported to our knowledge and could suggest that informant-reported SCD in men may be more reflective of pathological changes due to AD as compared to women. These results could be related to women being more likely to experience cognitive changes that are due to alternative etiologies (e.g., depression) and not sufficiently significant to produce objective changes on neuropsychological measures but are producing changes that are noticeable to an informant. Taken together, these results suggest that plasma p-tau181 is more strongly linked with objective cognition in women than subjective cognition in men.

This study has notable strengths including utilizing a comprehensive neuropsychological assessment with more granular measures of objective cognition that have been developed using sophisticated statistical techniques. The current study included measures of self- and informant-reported SCD, an early marker of increased risk for cognitive decline. Furthermore, the large sample size in this study allows for the examination of numerous potentially modifying factors, including cognitive diagnosis, *APOE* ε4 carrier status, age, and sex. Limitations include a lack of diversity in important factors, such as race/ethnicity and education in ADNI, thereby limiting generalizability. In addition, ADNI participants are relatively healthy; individuals with significant systemic illnesses are screened out. This limits generalizability to many individuals in the community with medical comorbidities that are known to influence blood biomarker values (e.g., chronic kidney disease).[50] Furthermore, neuropsychological composite scores, although advantageous in that they reduce the risk of type I error related to multiple comparisons, may have less sensitivity in preclinical disease states as compared to certain individual neuropsychological measures or process scores.

In sum, we found that plasma p-tau181 correlates with clinical changes that are typical of AD, thereby providing new evidence consistent with past work showing that this novel biomarker is useful in detecting clinical changes specific to AD pathology. In addition, we highlighted the specific demographic, diagnostic, and clinical factors that modify the association between plasma p-tau181 and cognition. These findings provide additional interpretive guidance to clinicians for using plasma p-tau181, should this biomarker make its way into clinical use. Women, younger individuals, and those with an increased genetic risk for AD show the strongest associations between plasma p-tau181 and cognition; p-tau181 results, if taken in isolation, may underestimate cognitive decline in individuals not belonging to these groups. Plasma p-tau181, assessed cross-sectionally, may be most clinically useful in individuals with some degree of objective cognitive impairment, although *APOE* ε4 carrier status, age, and sex should be considered when understanding these associations.

ACKNOWLEDGMENTS

Funding to support this work includes: K23-AG045966 (K.A.G.), R01-AG062826 (K.A.G.), R01-AG073439 (L.D.), F32-AG076276 (C.J.B.), K24-AG046373 (A.L.J.), and T32-AG058524 (C.J.B.). H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement #101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no. 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL (UKDRI-1003). Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and U.S. DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI

is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST STATEMENT

T.J.H. is a member of the scientific advisory board for Vivid Genomics (outside the work presented herein). H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). No other authors report any relevant conflicts. Author disclosures are available in the Supporting Information.

REFERENCES

1. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*. 2020;26(3):379-386. doi:10.1038/s41591-020-0755-1
2. Moscoso A, Grothe MJ, Ashton NJ, et al. Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum. *Brain*. 2021;144(1):325-339. doi:10.1093/brain/awaa399
3. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-433. doi:10.1016/S1474-4422(20)30071-5
4. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol*. 2021;78(4):396-406. doi:10.1001/jamaneurol.2020.4986
5. Blennow K. Plasma p-tau immunoassays, methodological aspects and clinical performance. *Alzheimers Dement*. 2020;16(S5):e037515. doi:10.1002/alz.037515
6. Sutterer MJ, Tranel D. Neuropsychology and cognitive neuroscience in the fMRI era: a recapitulation of localizationist and connectionist views. *Neuropsychology*. 2017;31(8):972-980. doi:10.1037/neu0000408
7. Wisdom NM, Mignogna J, Collins RL. Variability in Wechsler Adult Intelligence Scale-IV subtest performance across age. *Arch Clin Neuropsychol*. 2012;27(4):389-397. doi:10.1093/arclin/acs041
8. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging*. 2016;31(2):166-175. doi:10.1037/pag0000070
9. Rawle MJ, Davis D, Bendayan R, Wong A, Kuh D, Richards M. Apolipoprotein-E (Apoe) ε4 and cognitive decline over the adult life course. *Transl Psychiatry*. 2018;8(1):18. doi:10.1038/s41398-017-0064-8
10. Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(4):a006171. doi:10.1101/cshperspect.a006171
11. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol*. 1975;32(9):632-637. doi:10.1001/archneur.1975.00490510088009
12. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49. doi:10.1016/0022-3956(82)90033-4
13. Wechsler D. *Wechsler Memory Scale-Revised Manual*. The Psychological Corporation; 1987.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
15. Hughes CP, Berg L, Danziger W, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140(6):566-572. doi:10.1192/bjp.140.6.566
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944.
17. Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav*. 2012;6(4):502-516. doi:10.1007/s11682-012-9186-z
18. Rey A. *L'examen Clinique En Psychologie. [The Clinical Examination in Psychology]*. Presses Universitaries De France; 1958:222.
19. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364. doi:10.1176/ajp.141.11.1356
20. Gibbons LE, Carle AC, Mackin RS, et al. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav*. 2012;6(4):517-527. doi:10.1007/s11682-012-9176-1
21. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's disease centers' Uniform Data Set (UDS): the neuropsychological test battery. *Alzheimer Dis Assoc Disord*. 2009;23(2):91-101. doi:10.1097/WAD.0b013e318191c7dd
22. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Reitan Neuropsychology Laboratory; 1992.
23. Wechsler A. *Wechsler Adult Intelligence Scale-Revised*. Psychological Corporation; 1987.
24. Sunderland T, Hill JL, Mellow AM, et al. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. *J Am Geriatr Soc*. 1989;37(8):725-729.

25. Choi S, Mukherjee S, Gibbons LE, et al. Development and validation of language and visuospatial composite scores in ADNI. *Alzheimers Dement*. 2020;6(1):e12072. doi:10.1002/trc2.12072
26. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. PsycTESTS; 1983. doi:10.1037/t27208-000
27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
28. Farias ST, Mungas D, Reed BR, et al. The measurement of Everyday Cognition (ECog): scale development and psychometric properties. *Neuropsychology*. 2008;22(4):531-544. doi:10.1037/0894-4105.22.4.531
29. Salthouse TA. When does age-related cognitive decline begin?. *Neurobiol Aging*. 2009;30(4):507-514. doi:10.1016/j.neurobiolaging.2008.09.023
30. Levine DA, Gross AL, Briceño EM, et al. Sex differences in cognitive decline among US adults. *JAMA Netw Open*. 2021;4(2):e210169. doi:10.1001/jamanetworkopen.2021.0169
31. Alley D, Suthers K, Crimmins E. Education and cognitive decline in older Americans: results from the AHEAD sample. *Res Aging*. 2007;29(1):73-94. doi:10.1177/0164027506294245
32. Caselli RJ, Chen K, Locke DEC, et al. Subjective cognitive decline: self and informant comparisons. *Alzheimers Dement*. 2014;10(1):93-98. doi:10.1016/j.jalz.2013.01.003
33. Bretsky P, Guralnik JM, Launer L, Albert M, Seeman TE. MacArthur studies of successful aging. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur studies of successful aging. *Neurology*. 2003;60(7):1077-1081. doi:10.1212/01.wnl.0000055875.26908.24
34. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289-300.
35. Wang YL, Chen J, Du ZL, et al. Plasma p-tau181 level predicts neurodegeneration and progression to Alzheimer's dementia: a longitudinal study. *Front Neurol*. 2021;12:695696. doi:10.3389/fneur.2021.695696
36. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259.
37. Gharbi-Meliani A, Dugravot A, Sabia S, et al. The association of APOE ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alzheimers Res Ther*. 2021;13(1):5. doi:10.1186/s13195-020-00740-0
38. Baek MS, Cho H, Lee HS, Lee JH, Ryu YH, Lyoo CH. Effect of APOE ε4 genotype on amyloid-β and tau accumulation in Alzheimer's disease. *Alzheimers Res Ther*. 2020;12:140. doi:10.1186/s13195-020-00710-6
39. Thomas KR, Weigand AJ, Cota IH, et al. Intrusion errors moderate the relationship between blood glucose and regional cerebral blood flow in cognitively unimpaired older adults. *Brain Imaging Behav*. 2022;16(1):219-227. doi:10.1007/s11682-021-00495-8
40. Knopman DS, Caselli RJ. Appraisal of cognition in preclinical Alzheimer's disease: a conceptual review. *Neurodegener Dis Manag*. 2012;2(2):183-195. doi:10.2217/NMT.12.5
41. Clark C, Lewczuk P, Kornhuber J, et al. Plasma neurofilament light and phosphorylated tau 181 as biomarkers of Alzheimer's disease pathology and clinical disease progression. *Alzheimers Res Ther*. 2021;13:65. doi:10.1186/s13195-021-00805-8
42. Coomans EM, Verberk IMW, Ossenkoppele R, et al. A head-to-head comparison between plasma pTau181 and Tau PET along the Alzheimer's disease continuum. *J Nucl Med*. 2023;64(3):437-443. doi:10.2967/jnumed.122.264279
43. Rauchmann BS, Schneider-Axmann T, Perneczky R; Alzheimer's Disease Neuroimaging Initiative (ADNI). Associations of longitudinal plasma p-tau181 and NfL with tau-PET, Aβ-PET and cognition. *J Neurol Neurosurg Psychiatry*. 2021;92(12):1289-1295. doi:10.1136/jnnp-2020-325537
44. Therriault J, Benedet AL, Pascoal TA, et al. Association of plasma P-tau181 with memory decline in non-demented adults. *Brain Commun*. 2021;3(3):fcab136. doi:10.1093/braincomms/fcab136
45. Gerretsen P, Chung JK, Shah P, et al. Anosognosia Is an independent predictor of conversion from mild cognitive impairment to Alzheimer's disease and is associated with reduced brain metabolism. *J Clin Psychiatry*. 2017;78(9):805. doi:10.4088/JCP.16m11367
46. Barthélemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat Med*. 2020;26(3):398-407. doi:10.1038/s41591-020-0781-z
47. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain*. 2018;141(7):2181-2193. doi:10.1093/brain/awy146
48. Wattmo C, Wallin ÅK. Early-versus late-onset Alzheimer disease: long-term functional outcomes, nursing home placement, and risk factors for rate of progression. *Dement Geriatr Cogn Dis Extra*. 2017;7(1):172-187. doi:10.1159/000455943
49. Laws KR, Irvine K, Gale TM. Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry*. 2016;6(1):54-65. doi:10.5498/wjp.v6.i1.54
50. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2

SUPPORTING INFORMATION

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

How to cite this article: Bolton CJ, Steinbach M, Khan OA, et al.; for the Alzheimer's Disease Neuroimaging Initiative. Clinical and demographic factors modify the association between plasma phosphorylated tau-181 and cognition. *Alzheimer's Dement*. 2024;16:e70047. https://doi.org/10.1002/dad2.70047