JAMA Psychiatry | Brief Report

Psychosis in Alzheimer Disease and Elevations in Disease-Relevant Biomarkers

Jesus J. Gomar, PhD; Jeremy Koppel, MD

IMPORTANCE The emergence of psychotic symptoms in Alzheimer disease (AD) is associated with accelerated cognitive and functional decline that may be related to disease pathology.

OBJECTIVE To investigate the longitudinal dynamics of plasma tau phosphorylated at threonine 181 (p-tau181) and neurofilament light chain protein (NfL) levels in association with the emergence of psychotic symptoms (delusions and hallucinations) in the context of AD.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used longitudinal data from the Alzheimer Disease Neuroimaging Initiative (ADNI). Baseline analyses compared patients with mild cognitive impairment (MCI) and AD (both with psychosis [AD+P] and without psychosis [AD-P]) and participants who were cognitively unimpaired (CU). For the longitudinal analysis, participants with MCI and AD were subdivided into patients with evidence of psychosis at baseline (AD+P baseline) and patients free of psychosis at baseline who showed incidence of psychosis over the course of the study (AD+P incident). Study data were analyzed between June and November 2023.

EXPOSURES Plasma p-tau181 and NfL measures in individuals with MCI and AD, both with and without psychosis.

MAIN OUTCOMES AND MEASURES Plasma p-tau181 and NfL quantifications up to 48 months and concurrent assessments of presence or absence of delusions and hallucinations via the Neuropsychiatric Inventory (NPI) questionnaire.

RESULTS The cohort included 752 participants with AD (mean [SD] age, 74.2 [7.7] years; 434 male [57.7%]). A total of 424 CU participants had a mean (SD) age of 75.4 (6.6) years of whom 222 were female (52.4%). In the longitudinal analysis of p-tau181 trajectories of the AD+P group, the group of patients who showed incidence of psychosis over the course of follow-up (AD+P incident) demonstrated an associated increase in plasma p-tau181 levels compared with the group of patients who had psychosis at baseline (AD+P baseline) and showed an associated decrease in plasma p-tau181 levels ($F_{4, 117} = 3.24$; $P = .01$). The mean slope of p-tau181 change was significantly different in AD+P incident and AD+P baseline groups ($F_{5,746} = 86.76$, $P < .0001$) and when only individuals with amyloid-β positivity (Aβ+), which was determined using positron emission tomography, were compared ($F_{5,455} = 84.60$, $P < .001$). Patients who experienced psychosis at any time had increased levels of NfL relative to those who never experienced psychosis.

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest that the emergence of psychosis in AD was associated with elevations in plasma levels of p-tau181, highlighting the potential utility of plasma p-tau181 as a biomarker of neuropsychiatric illness in AD, which could have implications for predictive and treatment response strategies.

Supplemental content

Author Affiliations: Feinstein Institutes for Medical Research, Manhasset, New York (Gomar, Koppel); Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, New York (Koppel).

Corresponding Author: Jesus J. Gomar, PhD, Feinstein Institutes for Medical Research, 350 Community Dr, Manhasset, NY 11030 (jgomar@northwell.edu).

JAMA Psychiatry. 2024;81(8):834-839. doi:10.1001/jamapsychiatry.2024.1389
Published online June 26, 2024. Corrected on August 7, 2024.

Psychotic symptoms that occur in the context of Alzheimer disease (AD) dementia have an estimated prevalence of approximately 40%.[1] The emergence of psychotic symptoms including delusions and/or hallucinations in AD is associated with an accelerated cognitive and functional decline, caregiver burden, and a hastened mortality[2] that may reflect a more aggressive neurodegenerative process. Recently, we reported that increased retention of the tau positron emission tomography (PET) ligand fluorine 18 (^{18}F)-AV1451 (flortaucipir) is associated with psychosis in AD and a more rapid cognitive and functional decline.[3]

Minimally invasive, ultrasensitive plasma immunoassays that have increased accessibility and avoid the high cost of biomarker imaging have emerged as crucial tools to detect and track the progression of neuropathological processes associated with AD neurodegeneration.[4] Plasma tau phosphorylated at threonine 181 (p-tau181) is consistently increased early in AD. PET imaging studies have demonstrated that elevated plasma p-tau181 levels not only predict AD-associated tau pathology but are a very robust indicator of amyloid pathology as well.[5,6] Neurofilament light chain protein (NfL) is a cytoskeletal protein whose elevation in plasma is believed to be a marker of axonal damage found in a variety of neurodegenerative disorders, including AD.[7] It has very recently been reported that among diverse neurobehavioral impairments in AD, increases in plasma NfL level may be specifically associated with psychosis.[8] To our knowledge, no previously published studies have investigated the longitudinal association between levels of plasma p-tau181 and AD psychosis. In the current study, we investigated the longitudinal association between plasma levels of p-tau181 and NfL and the presence or emergence of delusions and hallucinations in AD to determine whether elevations in peripheral p-tau181 and NfL concentrations have utility as a biomarker of psychotic symptoms in AD.

Key Points

Question Are longitudinal changes in levels of plasma tau phosphorylated at threonine 181 (p-tau181) and neurofilament light chain protein (NfL) associated with the emergence of psychotic symptoms in the context of Alzheimer disease (AD)?

Findings In this cohort study of 752 patients with mild cognitive impairment (MCI) and AD, the emergence of psychotic symptoms (delusions and hallucinations) was associated with increases in plasma p-tau181 and NfL levels.

Meaning Findings suggest that plasma levels of p-tau181 and NfL may be used as a biomarker for psychosis in MCI and AD, with potential implications for disease monitoring and treatment strategies.

Methods

Participants

Participants from the Alzheimer Disease Neuroimaging Initiative (ADNI) with a diagnosis of AD or mild cognitive impairment (MCI) at baseline were included in the study. The data were downloaded in June 2023. Participants with MCI or AD were distributed in 2 groups according to presence or absence of psychosis via the Neuropsychiatric Inventory (NPI) presence of delusions or hallucinations: (1) participants with MCI and AD without psychosis over the course of the study (AD-P) and (2) participants with MCI and AD with psychosis at any time point over the course of the study (AD+P). An additional group of cognitively unimpaired (CU) participants was also included for comparative purposes on baseline assessments. To understand the longitudinal dynamics of p-tau181 level in association with psychosis in AD, we further subdivided the AD+P group into patients with MCI and AD who showed evidence of psychosis at baseline (AD+P baseline), and patients with MCI and AD who were free of psychosis at baseline and showed incidence of psychosis over the course of the study (AD+P incident). Regional ethical committees of all participating institutions approved the ADNI protocol. Participant race and ethnicity data were not gathered for this study because this information was not deemed relevant for the analyses/findings reported. All study participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Plasma p-Tau181 and NfL Quantifications

Plasma samples within ADNI were collected from 2007 through 2016. p-Tau181 levels were analyzed by the single molecule array (Simoa) technique (Quanterix Corp), using an in-house assay developed in the Clinical Neurochemistry Laboratory, University of Gothenburg, Gothenburg, Sweden. The assay uses a combination of 2 monoclonal antibodies (tau12 and AT270) and measures *N*-terminal to mid-domain forms of p-tau181[6]. NfL concentrations were also measured by Simoa platform using an in-house kit.[9] Longitudinal plasma p-tau181 and NfL quantifications were monitored for up to 48 months of follow-up and were log transformed for all the analyses.

Statistical Analysis

Comparisons between groups at baseline in continuous demographic and clinical status variables were performed using generalized linear models (GLMs) adjusted for multiple comparisons using Bonferroni correction, and χ^2 tests were used for comparisons in categorical variables. A linear mixed-effects (LME) model was fit to analyze the longitudinal p-tau181 trajectories in the AD+P subgroups, AD+P baseline group, and AD+P incident group with random intercepts and slopes. LME analyses included age, sex, and education as covariates, using residual (restricted) maximum likelihood estimation and assuming an unstructured covariance matrix. Plasma p-tau181 rate of change within groups (β slopes) was computed as averaged individual slopes from LME models that included random intercepts and slopes. All *P* values were 2-sided, and $P < .05$ was considered statistically significant. Data analysis was performed using SAS Studio, version 9.04.01 (SAS Institute).

Table. Demographic, Biomarker, and Clinical Characteristics

Variable	CU (n = 424)	AD-P (n = 631)	AD+P incident (n = 73)	AD+P baseline (n = 48)	Statistical test	*P* value	Post hoc comparison (Bonferroni adjusted)
Age, mean (SD), y	75.37 (6.61)	73.44 (8.06)	73.14 (8.14)	76.05 (6.92)	$F_{3, 1172} = 7.00$	<.001	CU>AD-P[a] CU>AD+P incident[b] AD-P < AD+P baseline[b] AD+P incident<AD+P baseline[b]
Sex, male/female (% male)	202/222 (47.6)	368/263 (58.3)	40/33 (54.8)	26/22 (54.2)	$\chi^2 = 11.66$	.009	CU vs AD-P[a]
Education, mean (SD), y	16.55 (2.59)	16.04 (2.75)	15.63 (2.55)	15.75 (2.97)	$F_{3, 1172} = 4.65$	.003	CU>AD-P[b] CU>AD+P incident[b]
Plasma p-tau181, mean (SD), pg/mL[c,d]	15.20 (8.61)	18.90 (10.19)	21.17 (9.41)	25.73 (11.24)	$F_{6, 1169} = 22.85$	<.001	CU<AD-P[a] CU<AD+P incident[a] CU<AD+P baseline[a] AD-P < AD+P incident[b] AD-P < AD+P baseline[a]
Plasma NfL, mean (SD) [No.], pg/mL[c,d]	38.05 (17.57) [421]	40.67 (19.48) [623]	45.39 (19.53) [72]	50.32 (17.93) [47]	$F_{6, 1156} = 88.87$	<.001	CU<AD-P[a] CU<AD+P incident[a] CU<AD+P baseline[a] AD-P < ADP incident[e] AD-P < AD+P baseline[e]
APOE ε4 allele carriers, No. (%)	114 (26.9)	291 (46.1)	50 (68.5)	34 (70.8)	$\chi^2 = 81.71$	<.001	CU<AD-P[a] CU<AD+P incident[a] CU<AD+P baseline[a] AD-P < ADP incident[a] AD-P < AD+P baseline[a]
Aβ status, negative/positive (% positive)[f]	205/181 (46.89)	226/363 (61.63)	8/60 (85.24)	1/38 (97.44)	$\chi^2 = 73.06$	<.001	CU<AD-P[a] CU<AD+P incident[a] CU<AD+P baseline[a] AD-P < ADP incident[a] AD-P < AD+P baseline[a]
CDR-SB, mean (SD)[c]	0.16 (0.66)	2.23 (2.17)	3.83 (2.29)	5.40 (3.03)	$F_{6, 1169} = 119.33$	<.001	CU<AD-P[a] CU<AD+P incident[a] CU<AD+P baseline[a] AD-P < AD+P incident[a] AD-P < AD+P baseline[a] AD+P incident<AD+P baseline[a]
MMSE, mean (SD) [No.][c]	28.95 (1.34) [423]	26.72 (3.31)	25.45 (3.37)	22.63 (5.41)	$F_{6, 1168} = 65.13$	<.001	CU>AD-P[a] CU>AD+P incident[a] CU>AD+P baseline[a] AD-P > AD+P incident[a] AD-P > AD+P baseline[a] AD+P incident>AD+P baseline[a]

Abbreviations: Aβ, amyloid β; AD+P, Alzheimer disease with psychosis; AD-P, Alzheimer disease without psychosis; CDR-SB, Clinical Dementia Rating Sum of Boxes; CU, cognitively unimpaired; GLM, generalized linear model; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain protein; p-tau181, tau phosphorylated at threonine 181; PET SUVR, positron emission tomography standardized uptake value ratio.

[a] $P < .001$.

[b] $P < .05$.

[c] GLM adjusted by age, sex, and education.

[d] Plasma p-tau181 and NfL log transformed values were used in the GLM analysis.

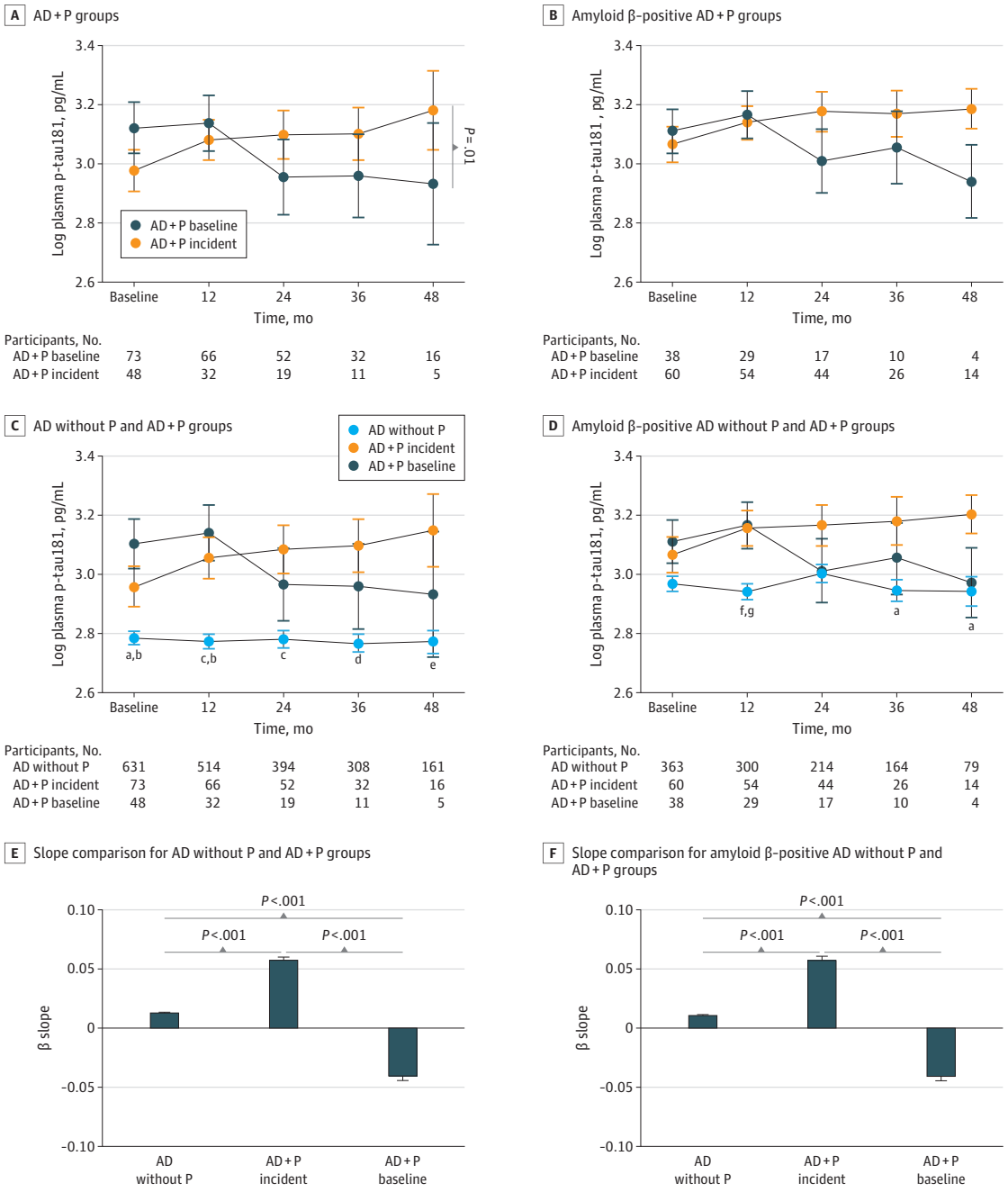
[e] $P < .01$.

[f] Based on florbetapir (AV45) PET SUVR greater than 1.11 or florbetaben (FBB) PET SUVR greater than 1.08 at any time point along the study.

Results

The cohort included 752 participants with AD (mean [SD] age, 74.2 [7.7] years; 318 female [42.3%]; 434 male [57.7%]). An additional group of 424 CU participants (mean [SD] age, 75.4 (6.6) years; 222 female [52.4%]; 202 male [47.6%]) were also included in the study. The demographic and clinical description of the groups is in the **Table**. At baseline, AD+P participants (those who already had psychosis and those destined to develop psychosis over the course of study follow-up) had elevations of plasma p-tau181 and NfL levels. Specifically, AD+P participants (both at baseline and incident) had significantly increased levels of p-tau181 and NfL compared with both CU and AD-P groups, whereas the AD-P group had higher p-tau181 and NfL levels than the CU group (p-tau181 post hoc Bonferroni-adjusted statistical comparison of $P < .001$ and NfL post hoc Bonferroni-adjusted statistical comparison of $P < .001$) (eFigure in Supplement 1). Separating those who had psychosis at the baseline visit in the AD+P group from those who did not have psychosis but would develop it over the course of follow-up (incident psychosis) revealed that the emergence of psychosis was associated with increases in p-tau181 level building toward the psychotic episode, whereas those who already had psychosis exhibited declining p-tau181 levels over time (**Figure 1**, A) ($F_{4, 117} = 3.24$; $P = .01$), a trend that was not significant when including only those with imaging evidence of amyloid positivity (Figure 1, B). In the complete AD sample, p-tau181 levels in those with no psychosis over the course of the study (AD-P) remained lower and did not exhibit significant changes over time relative to the AD+P groups (Figure 1, C), an outcome that was diminished in those with confirmed amyloid positivity (Figure 1, D). The

Figure 1. Longitudinal Plasma Phosphorylated Tau 181 (p-Tau181) Levels



A, Longitudinal plasma p-tau181 comparison between Alzheimer disease (AD) + psychosis (P) groups. B, Longitudinal plasma p-tau181 comparison between amyloid-β positive (Aβ+) AD+P groups. C, Longitudinal plasma p-tau181 comparison between AD-P and AD+P groups. D, Longitudinal plasma p-tau181 comparison between amyloid-β positive (Aβ+) AD-P and AD+P groups. Log-transformed values were used in the statistical analysis. For panels A-D, lines represent least square means (LSM), and error bars represent SEs of the mean from the linear mixed-effects model. E, Mean β slope comparison between AD-P, AD+P incident, and AD+P baseline groups. F, Mean β slope comparison between amyloid-β (Aβ+) AD-P, AD+P incident, and AD+P baseline groups. For panels E-F, bars represent LSM from the generalized linear model analysis adjusted by age at baseline, sex, and education. Error bars represent SE of the mean. AD+P baseline indicates AD with psychosis at baseline; AD+P incident indicates AD with incident psychosis; AD-P indicates AD without psychosis.

[a]AD-P vs AD+P incident $P < .05$.

[b]AD-P vs AD+P baseline $P = .001$.

[c]AD-P vs AD+P incident $P < .001$.

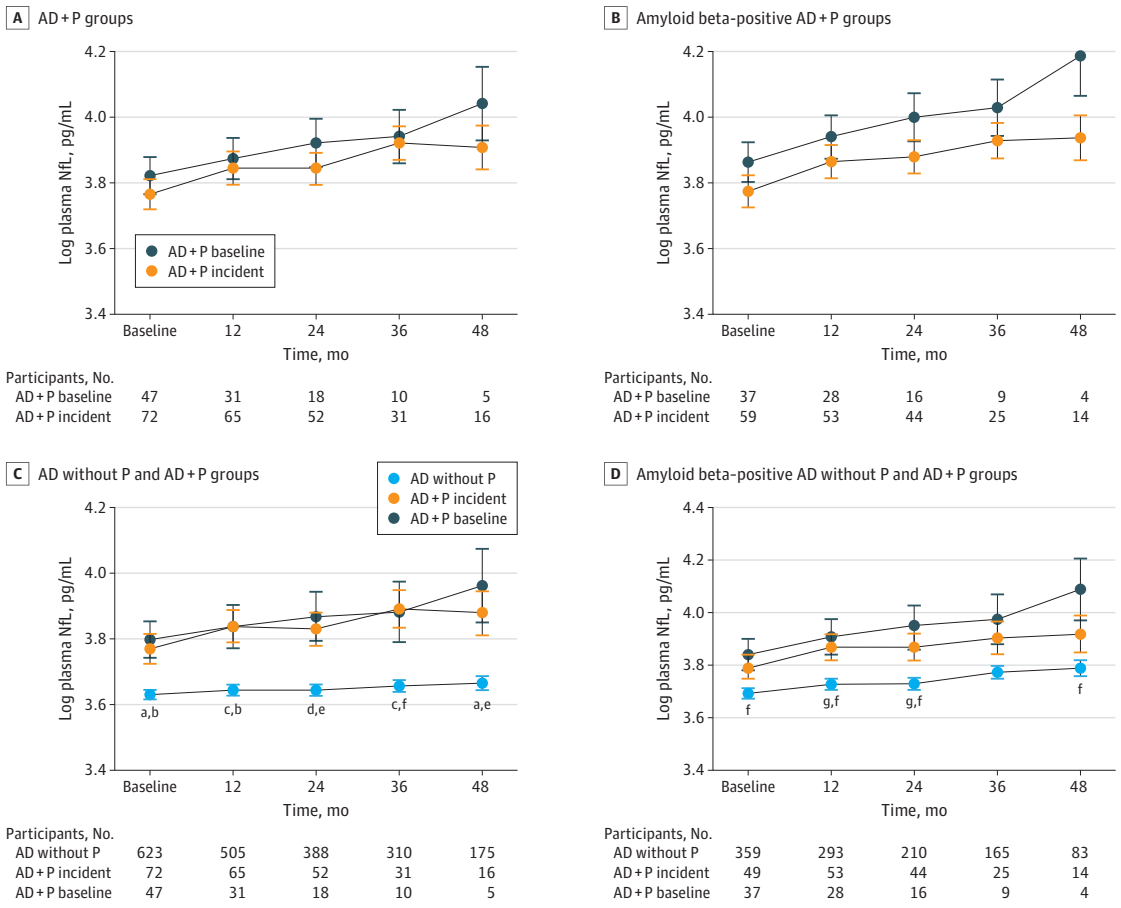
[d]AD-P vs AD+P incident $P = .001$.

[e]AD-P vs AD+P incident $P < .01$.

[f]AD-P vs AD+P incident $P = .01$.

[g]AD-P vs AD+P baseline $P < .05$.

Figure 2. Longitudinal Plasma Neurofilament Light Chain Protein (NfL) Levels



A, Longitudinal plasma NfL level comparison between Alzheimer disease (AD) + psychosis (P) groups. B, Longitudinal plasma NfL level comparison between amyloid-β positive (Aβ+) AD+P groups. C, Longitudinal plasma NfL level comparison between AD-P and AD+P groups. D, Longitudinal plasma NfL level comparison between amyloid-β positive (Aβ+) AD-P and AD+P groups. For panels A-D, log-transformed values were used in the statistical analysis. Lines represent least square means, and error bars represent SEs of the mean from the linear mixed-effects model. AD+P baseline indicates AD with psychosis at baseline; AD+P incident indicates AD with incident psychosis; AD-P indicates AD without psychosis.

[a]AD-P vs AD+P incident $P < .01$.
[b]AD-P vs AD+P baseline $P = .01$.
[c]AD-P vs AD+P incident $P < .001$.
[d]AD-P vs AD+P incident $P = .001$.
[e]AD-P vs AD+P baseline $P < .01$.
[f]AD-P vs AD+P baseline $P < .05$.
[g]AD-P vs AD+P incident $P < .05$.

difference in the p-tau181 slopes between these 3 groups was statistically significant ($F_{5,746} = 86.76$; $P < .001$) (Figure 1, E), including in those with confirmed amyloid positivity ($F_{5,455} = 84.60$; $P < .001$), corroborating the different longitudinal trajectories in plasma p-tau181 level between the AD groups with psychosis at baseline and incident psychosis and between those with and without psychosis at any time. Although there were no significant differences in plasma levels of NfL between those with baseline and incident psychosis (**Figure 2**, A and B), those who had psychosis at any time had increased levels of NfL relative to those who never had psychosis (Figure 2, C), an outcome similarly diminished by amyloid positivity (Figure 2, D). More details on study data analyses and results are available in the eAppendix in Supplement 1.

Discussion

This cohort study revealed that those with AD who already had or would develop psychosis over the course of longitudinal follow-up had associated cross-sectional elevations in the plasma concentration of p-tau181 and NfL in comparison with those with AD who did not have psychosis. Additionally, the longitudinal trajectories of plasma p-tau181 levels distinguished those who already had psychosis at baseline from those who would develop psychosis, with concentrations building before the onset of psychosis and then declining. The outcomes were diminished when including only those with amyloid positivity. This may reflect the inadvertent inclusion of those with other p-tau181-impacting

amnestic tauopathies that could be confused with mild AD, such as primary age-related tauopathy,[10] in which plasma p-tau181 levels have recently been shown to be lower than in AD.[11]

Strengths and Limitations

The strengths of this study were the detailed clinical characterization of the sample and longitudinal quantifications of plasma proteins over 4 years. One limitation was the lack of availability of plasma levels of p-tau217 in the current sample, as p-tau217 has been shown to have increased specificity in distinguishing AD from other tauopathies.[11]

Conclusions

The results of this retrospective longitudinal cohort study suggest that the emergence of psychosis in AD was associated with elevations in plasma levels of p-tau181, indicating that p-tau181 may have value as a biomarker of neuropsychiatric illness in AD.

ARTICLE INFORMATION

Accepted for Publication: April 4, 2024.

Published Online: June 26, 2024. doi:10.1001/jamapsychiatry.2024.1389

Correction: This article was corrected on August 7, 2024, to fix the title of Figure 1.

Author Contributions: Dr Gomar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Koppel.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical review of the manuscript for important intellectual content: Koppel.
Statistical analysis: Gomar.
Administrative, technical, or material support: Koppel.
Supervision: All authors.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grant 1 K01 AG078496-01 from the National Institute of Aging and grant AARGD-22-917772 from Alzheimer's Association (Dr Gomar); grant 1 R21 MH135148-01 from the National Institute of Mental Health (Dr Koppel), and Alzheimer's Foundation of America. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health grant U19 AG024904) and 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, Biogen, Bristol Myers Squibb, CereSpir, Cogstate, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, Euroimmun, F. Hoffmann-La Roche and its affiliated company Genentech, Fujirebio, GE Healthcare, IXICO, Janssen Alzheimer Immunotherapy Research & Development, Johnson & Johnson Pharmaceutical Research & Development, Lumosity, Lundbeck, Merck & Co, Meso Scale Diagnostics, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer, 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.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Ismail Z, Creese B, Aarsland D, et al. Psychosis in Alzheimer disease—mechanisms, genetics, and therapeutic opportunities. *Nat Rev Neurol*. 2022;18(3):131-144. doi:10.1038/s41582-021-00597-3

2. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry*. 2005;162(11):2022-2030. doi:10.1176/appi.ajp.162.11.2022

3. Gomar JJ, Tan G, Halpern J, Gordon ML, Greenwald B, Koppel J. Increased retention of tau PET ligand [^{18}F]-AV1451 in Alzheimer disease psychosis. *Transl Psychiatry*. 2022;12(1):82. doi:10.1038/s41398-022-01850-z

4. d'Abramo C, D'Adamio L, Giliberto L. Significance of blood and cerebrospinal fluid biomarkers for Alzheimer disease: sensitivity, specificity and potential for clinical use. *J Pers Med*. 2020;10(3):116. doi:10.3390/jpm10030116

5. Mielke MM, Hagen CE, Xu J, et al. Plasma phospho-tau181 increases with Alzheimer disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement*. 2018;14(8):989-997. doi:10.1016/j.jalz.2018.02.013

6. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer disease: a diagnostic performance and prediction modeling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-433. doi:10.1016/S1474-4422(20)30071-5

7. Mattsson N, Andreasson U, Zetterberg H, Blennow K. Alzheimer's Disease Neuroimaging Initiative. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2017;74(5):557-566. doi:10.1001/jamaneurol.2016.6117

8. Huang L, Huang Q, Xie F, Guo Q. Neuropsychiatric symptoms in Alzheimer continuum and their association with plasma biomarkers. *J Affect Disord*. 2024;348:200-206. doi:10.1016/j.jad.2023.12.062

9. Rohrer JD, Woollacott IO, Dick KM, et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. *Neurology*. 2016;87(13):1329-1336. doi:10.1212/WNL.0000000000003154

10. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*. 2014;128(6):755-766. doi:10.1007/s00401-014-1349-0

11. Yu L, Boyle PA, Janelidze S, et al. Plasma p-tau181 and p-tau217 in discriminating PART, AD, and other key neuropathologies in older adults. *Acta Neuropathol*. 2023;146(1):1-11. doi:10.1007/s00401-023-02570-4