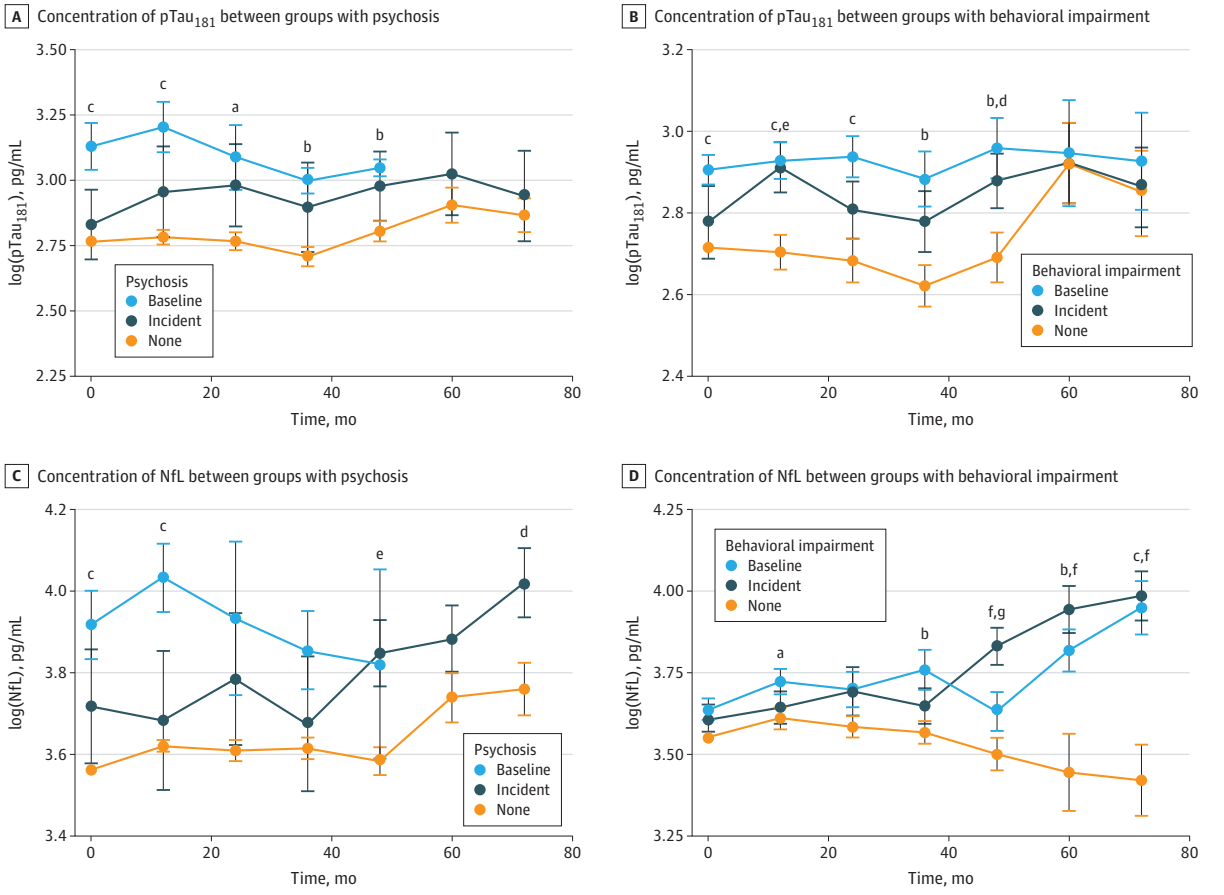
RESEARCH LETTER

Alzheimer Disease–Relevant Biomarker Elevations in Psychosis and Broad Neuropsychiatric Impairment

Among neuropsychiatric symptoms (NPS) in Alzheimer disease (AD), psychosis appears uniquely impactful, conferring the greatest risk and rapidity of cognitive decline and earlier death.[1-3] On neuroimaging, psychotic symptoms correlate with smaller total brain volume and specific patterns of increased tau deposition in AD.[2,4] Neuropathological studies demonstrate more advanced neurofibrillary (tau) tangles and hyperphosphorylated tau deposition in patients with AD with psychosis.[3,5] This supports a growing hypothesis that psychotic symptoms signal a more aggressive AD phenotype, driven by region-specific tau pathology. Importantly, Gomar and Koppel[6] recently demonstrated that emergence of psychotic symptoms in AD corresponds with longitudinal increases in serum levels of hyperphosphorylated tau ($pTau_{181}$) and neurofilament light chain (NfL). While this bears important implications for understanding psychosis in AD, its association with tau pathology, longitudinal disease course, and transdiagnostic psychotic phenomena (ie, the degree to which

Supplemental content

Figure. Longitudinal Trajectories of Plasma Biomarker Concentrations Within Psychosis and Behavioral Impairment Groups



Longitudinal trajectories of log-transformed concentrations of plasma biomarkers (A and B: hyperphosphorylated tau protein at the threonine 181 position [$pTau_{181}$]; C and D: neurofilament light chain [NfL]) between groups with symptom of interest (either psychosis [A and C], or behavioral impairment [B and D]) at baseline (baseline group, light blue), with symptom onset during the study period (incident group, dark blue), and with no symptoms during the study period (none group, orange) over time (in months). Between-group differences at individual time points assessed using the Welch *t* test.

[a] $P < .05$ baseline group vs none group.

[b] $P < .01$ baseline group vs none group.

[c] $P < .001$ baseline group vs none group.

[d] $P < .05$ incident group vs none group.

[e] $P < .01$ incident group vs none group.

[f] $P < .001$ incident group vs none group.

[g] $P < .05$ incident group vs baseline group.

Table. Effects of Symptom Group on Plasma Biomarker Concentrations on Longitudinal Mixed-Effects Modeling

Plasma biomarker	Variable	Estimate, β (95% CI)[a] Unadjusted	Adjusted
$pTau_{181}$			
Psychosis	Incident	0.0801 (−0.1378 to 0.2984)	0.075 (−0.133 to 0.284)
	Baseline	0.4121 (0.1551 to 0.6689)[b]	0.228 (−0.017 to 0.473)
	Incident*time	0.0002 (−0.0031 to 0.0035)	0.000 (−0.003 to 0.004)
	Baseline*time	−0.0037 (−0.0121 to 0.0048)	−0.003 (−0.011 to 0.006)
Behavioral impairment	Incident	0.0865 (−0.0499 to 0.2231)	0.078 (−0.520 to 0.209)
	Baseline	0.1949 (0.0884 to 0.3014)[b]	0.113 (0.009 to 0.215)[b]
	Incident*time	0.0004 (−0.0018 to 0.0025)	0.000 (−0.002 to 0.002)
	Baseline*time	0.0000 (−0.0020 to 0.0021)	0.001 (−0.001 to 0.003)
NfL			
Psychosis	Incident	0.0560 (−0.1106 to 0.2073)	0.056 (−0.088 to 0.200)
	Baseline	0.1435 (0.1183 to 0.5046)[b]	0.144 (−0.025 to 0.312)
	Incident*time	0.0032 (0.0010 to 0.0061)[b]	0.003 (0.001 to 0.006)[b]
	Baseline*time	−0.0016 (−0.0081 to 0.0041)	−0.002 (−0.008 to 0.004)
Behavioral impairment	Incident	0.1207 (0.0202 to 0.2221)[b]	0.067 (−0.023 to 0.157)
	Baseline	0.0705 (−0.0092 to 0.1502)	0.020 (−0.051 to 0.091)
	Incident*time	0.0035 (0.0019 to 0.0052)[b]	0.003 (0.002 to 0.005)[b]
	Baseline*time	0.0038 (0.0023 to 0.0054)[b]	0.004 (0.002 to 0.006)[b]

Abbreviations: NfL, neurofilament light chain; $pTau_{181}$, hyperphosphorylated tau protein at the threonine 181 position.

[a] Estimates of fixed effects (β) and 95% confidence intervals for effect of symptom group (either incident during the study period or present at baseline evaluation compared to those without symptom of interest throughout the study period for both psychosis and behavioral impairment) and symptom group interaction with time on plasma biomarkers (both pTau181 and NfL) for longitudinal mixed-effects models. Models included random effects of intraparticipant variability (both intercept and slope over time), as well as fixed effects of time, participant age at baseline, years of education, sex, and cognitive diagnosis at baseline (either mild cognitive impairment or Alzheimer disease). Interactions are denoted by * symbol.

[b] Significant (confidence intervals do not include 0).

these biomarker elevations are specific to psychosis vs neurobehavioral dysfunction more broadly) remains unknown. Clarifying this association is essential to understanding the association between specific AD-related NPS and their neuropathologic correlates.

Methods | Study participants in the Alzheimer's Disease Neuroimaging Initiative with clinician-diagnosed mild cognitive impairment (MCI) or AD at baseline, available serum $pTau_{181}$ or NfL data, and Neuropsychiatric Inventory Questionnaire (NPI-Q) data were included. Informed consent and institutional review board approval were obtained (see the eMethods in Supplement 1). Psychosis was defined as the presence of either hallucinations or delusions on the NPI-Q. Behavioral impairment was defined as an NPI-Q total score of 3 or higher. Additional sensitivity analyses were conducted including only nonpsychotic NPI-Q items (excluding delusions and hallucinations) when calculating NPI-Q total score. For psychosis and behavioral impairment separately, participants were grouped in the following categories by symptom course for analysis: (1) absence of symptoms of interest throughout the study period; (2) symptoms initially absent, later incident during the study course; or (3) symptoms present at baseline assessment. $pTau_{181}$ and NfL were obtained as described elsewhere.[6] Linear mixed-effects models of longitudinal serum biomarker concentrations ($pTau_{181}$ and NfL) were constructed adjusting for baseline age, cognitive diagnosis (baseline MCI or AD), years of education, and sex. Between-group differences at individual time points were evaluated using the Welch *t* test. Further details are provided in the eMethods in Supplement 1.

Results | A total of 731 participants (305 female [41.7%]; mean [SD] age, 72.18 [7.57] years; mean [SD] years of education, 15.98 [2.77] years) met inclusion criteria (psychosis groups: none [n = 641], incident [n = 56], and baseline [n = 22]; behavioral impairment groups: none [n = 296], incident [n = 149], and baseline [n = 228]; see the eTable in Supplement 1). Both baseline psychosis and baseline behavioral impairment groups demonstrated elevated baseline $pTau_{181}$ (**Figure**). Only the baseline psychosis group demonstrated elevated baseline NfL (Figure). Mixed-effects modeling demonstrated that baseline psychosis was associated with $pTau_{181}$ and NfL only in unadjusted models (**Table**), multivariate sensitivity analyses removing baseline cognitive diagnosis, and additional sensitivity analysis including only participants with baseline MCI. Baseline behavioral impairment was associated with increased longitudinal $pTau_{181}$ (Table). Incident psychosis and behavioral impairment demonstrated interaction effects with time on longitudinal NfL. Baseline behavioral impairment also demonstrated an interaction effect with time on NfL. Group differences are reported relative to corresponding "none" symptom group. Sensitivity analyses excluding psychotic symptoms from behavioral impairment measure did not affect any reported associations.

Discussion | Consistent with a prior report,[6] psychosis was positively associated with serum $pTau_{181}$ and NfL, although similar associations were observed with other NPS more broadly (and were not predominately driven by psychotic symptoms on sensitivity analyses). Similarly, baseline psychosis did not predict longitudinal $pTau_{181}$ elevation after adjusting for baseline cognitive diagnosis. Key limitations include relatively few participants with psychosis, increasing risk of type II error. Collectively, this suggests that the association between psychosis and plasma biomarkers may not be specific to psychosis, but rather may also be seen in sufficiently severe neuropsychiatric dysfunction more broadly. As reported by Gomar and

Koppel,[6] elevations in plasma biomarkers may correspond more closely with onset of psychosis compared to other NPS, although further work is required to directly evaluate this important nuance.

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Concept and design: Bray, Morrow, Onyike.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bray, Shaw, Morrow.
Critical review of the manuscript for important intellectual content: All authors.
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Group Information: The Alzheimer's Disease Neuroimaging Initiative members appear in Supplement 2.

Data Sharing Statement: See Supplement 3.

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